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**14. ABSTRACT (200 words)**

The ***M3I-ICHP*** aims to lead the way in Cardiovascular Disease (CVD) Prevention by conducting novel research utilizing a Systems Biology / personalized medicine design to discover and develop practical, effective and preemptive integrative approaches in order to detect and combat CVD earlier before it affects the quality of life. ICHP's ultimate goal is to translate our evidenced-based research findings for application into clinical practice. A translational research approach will provide the ability to find novel disease markers, optimal prevention and holistic treatment approaches, and a unique venue for future research as the "virtual laboratory" for optimal comprehensive health prevention in the military beneficiary population. This research method also allow us to further hypothesize and define relationships between CVD, other cardio metabolic disease states and maladaptive behavior patterns unique to service members such as pre-diabetes, stress, overweight and sleep disorders with the aim of targeting these disorders in a pre-clinical phase. Using an integrative, interdisciplinary preventive health approach, ICHP has shown that an individual's cluster of CV risk factors can be effectively targeted and improved.

**15. SUBJECT TERMS**
Lifestyle; Cardiac Prevention; Behavior; Coronary Heart Disease (CHD); Proteomics; Genomics; Metabolic Syndrome; Cardiovascular Disease (CVD); Diabetes; Obesity; Stress

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**Executive Summary – Final Report**

***Military Molecular Medicine Initiative (M3I)-Integrative Cardiac Health Project (ICHP)***

The ***M3I-ICHP*** aims to lead the way in Cardiovascular Disease (CVD) Prevention by conducting novel research utilizing a Systems Biology / personalized medicine design to discover and develop practical, effective and preemptive integrative approaches in order to detect and combat CVD earlier before it affects the quality of life. ICHP's ultimate goal is to translate our evidenced-based research findings for application into clinical practice. In keeping with this aim, collaborative research efforts have continued between ICHP projects at Walter Reed Army Medical Center, Windber Research Institute and Windber Medical Center. In the past year, the following key accomplishments are noted:

- Total visits in WRAMC Cardiovascular Prevention / Windber Cardiovascular Risk Clinic (CPP)/CRC Programs this year: 1975
- Enrollment complete: 2 protocols (data analysis in progress); Active protocols: 8
- Dissemination of scientific research findings:
    - Manuscript published: 1; Submitted for publication: 2; Manuscripts in preparation: 4
    - Presentations at regional/national meetings: 11; Abstracts submitted for presentation: 4
- Relevant findings in our population include:
    - Incorporating novel risk factors such as those proposed in the ICHP developed risk score and considering the value of family history may significantly improve the predictive accuracy of CVD risk assessment and may reveal appropriate targets for therapeutic intervention.
    - Lifestyle intervention can lead to atherosclerosis regression, but may depend on the extent of CV health measures achieved.
    - In motivated, *at risk* patients, an intensive lifestyle change program can effectively alter traditional CAD risk factors and produce dramatic reductions in plasma insulin and leptin levels.
    - Principal component analysis showed clear differences in metabolite abundance during a lifestyle program and distinct profiles of metabolite change in participants with diagnosed heart disease compared to those with only elevated risk factors.
    - Assessing stress levels in patients may provide targets for intervention in stroke prevention. High stress is associated with numerous behavioral, biochemical and anthropometric factors that increase stroke risk. Comprehensive stroke risk prevention could benefit from an integrative approach that includes lifestyle behavioral assessment to identify as well as to reduce stroke risk and improve quality of life indicators.
    - Participants who slept longer showed a better CV risk profile and enjoyed higher quality of life by a number of indicators. Despite a lack of difference in the more traditional risk factors, total sleep time is strongly associated with lower stress, healthier body weight, and lower inflammation. These findings underscore the importance of addressing adequate sleep time as a modifiable risk factor in an integrative program for CV risk reduction.
    - High stress correlates with numerous unhealthy metabolic states which place patients at higher risk for CV disease. Prediabetic patients can significantly improve their CV risk profile by reducing stress. We hypothesize that an integrative lifestyle change program may interrupt the negative sequence of events caused by CRF and potentially provide prediabetic patients an adjunct to their CV risk reduction action plan.
    - High stress correlates with numerous unhealthy metabolic states which place patients at higher risk for CV disease. Prediabetic patients can significantly improve their CV risk profile by reducing stress. We hypothesize that an integrative lifestyle change program may interrupt the negative sequence of events caused by CRF and potentially provide prediabetic patients an adjunct to their CV risk reduction action plan.

## Introduction

The primary vision of the ***Military Molecular Medicine Initiative (M3I)-Integrative Cardiac Health Project*** is to is to lead the way in Cardiovascular Disease (CVD) Prevention by conducting novel research utilizing a Systems Biology / personalized medicine design to discover and develop practical, effective and preemptive integrative approaches in order to detect and combat CVD earlier before it affects the quality of life. ICHP's ultimate goal is to translate our evidenced-based research findings for application into clinical practice in an effort to achieve the following research aims:

- ❑ Improve Force Health by better understanding the CVD risk susceptibility of military specific populations as well as to understand the individual service member through leading-edge research using novel tools and technologies. Synchronize our programs with existing DOD efforts in Comprehensive Soldier Fitness (CSF), Comprehensive Behavioral Health System of Care (CBHSOC) and the Warrior Resiliency Program.
- ❑ Investigate and create transformational models of healthcare delivery through personalized CVD prevention tracks as an adjunct to traditional care.
- ❑ Refine individualized prevention strategies through statistical data modeling to define the most cost-effective and sustainable approaches in promoting cardiovascular health throughout the military lifecycle.
- ❑ Simultaneously, improve understanding of the molecular, physiological, biochemical, immunological and environmental basis of CV health and disease and to use that understanding to develop improved approaches to disease diagnosis, treatment and prevention, in line with NHLBI Strategic Plan 2008.

## Body

Completed tasks or tasks removed from SOW during this reporting period are not reflected in the Gantt charts submitted with this report.

**Task #1: Complete data analysis of "Non-Invasive Coronary Artery Disease Reversal" (CADRe) Study Protocol conducted at WRAMC.**

**Status:** Task complete. Study design and methodology described in previous reports. Study demographics and major outcomes have been published (see Appendix A). The following final manuscript has been submitted for publication (see Appendix A):

Marshall, DA, Walizer, EM, & Vernalis, MN. Effect of a One-Year Lifestyle Intervention Program on Carotid Intima Media Thickness, *Military Medicine*.

**Task #3: Ongoing data collection for "CADRe Five-Year Follow-up" Protocol.**

**Status:** WRAMC HUC approved this study on 23 May 2006. Protocol was approved by the US Army Medical Department Center and School, Clinical Investigations Regulatory Office (CIRO) on 2 November 06. The MRMC Memorandum of Deferral was received 22 Jan 07. Change of PI to COL Randolph Modlin, Chief, WRAMC Cardiology, was approved 3 December 2008. Study addendums have been previously reported. The annual Continuing Review was approved by WRAMC DCI HUC on 27 April 2010. This study is now closed to enrollment, data collection is complete and final data reconciliation and analysis is in progress. Publication plan in progress.

Study Design and Objectives

This follow-up study will determine the persistence of healthy lifestyle behavioral changes and CVD risk factor control results after their original CADRe study participation. This study will continue as a longitudinal observational study where patients will have yearly follow-up visits at 1, 2, 3, 4, and 5 years after completion or expected completion of the CADRe Study. This study will involve prospective collection of data, however, there will be no tests ordered that are not considered WRAMC Cardiology standard of care for the study population identified. Therefore, there are no risks involved with this study outside those of the standard of care treatment. Specific aims are to determine:

1. Persistence of lifestyle change behaviors in diet, exercise, and stress management
2. Coronary risk-factor control
3. Quality of Life

Hypothesis

Subjects who have been exposed to an intensive lifestyle change program will demonstrate long-term carryover of heart healthy characteristics including persistence of favorable lifestyle change behaviors and risk factor control.

Recruitment/Enrollment

Up to 163 male and female CADRe study participants, age 18 years or older, with subsequent completion of Phase 1 of the CADRe Study (3-month data collection) were recontacted and invited to participate in this five (5) year follow-up study (post-study completion or expected completion). Because of the timing of this protocol submission, the earlier cohorts did not have as many yearly follow-up periods as the later cohorts (See Table 1).

**Table 1. Projected Longitudinal Follow-Up of CADRe Study**

| Cohort # | Completers (≥ 12 weeks of intervention) | Dropouts (< 12 week exposure) | No longer available | Available to enroll | Available Follow-Up | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1-Yr | 2-Yr | 3-Yr | 4-Yr | 5-Yr |
| 1 | 7 | 3 | | 7 | | | | | X |
| 2 | 16 | 2 | 1 | 15 | | | | | X |
| 3 | 15 | 5 | 1 | 14 | | | | | X |
| 4 | 18 | 2 | 1 | 17 | | | | X | X |
| 5 | 12 | 1 | | 12 | | | | X | X |
| 6 | 19 | | | 19 | | | | X | X |
| 7 | 15 | 5 | | 15 | | | X | X | X |
| 8 | 12 | 4 | | 12 | | | X | X | X |
| 9 | 9 | 2 | | 9 | | | X | X | X |
| 10 | 10 | | | 10 | | X | X | X | X |
| 11 | 11 | 1 | | 11 | | X | X | X | X |
| 12 | 10 | 4 | | 10 | | X | X | X | X |
| 13 | 12 | 5 | | 12 | X | X | X | X | X |
| Totals | 166 | 34 | 3 | 163 | 12 | 43 | 79 | 127 | 163 |

Primary Outcome Measure - Heart Health Index (HHI)

A composite index of 7 heart healthy characteristics (BMI 18.5 – 25; LDL-cholesterol < 100 mg/dL; dietary fiber intake ≥ 25 gms/day; consumption of 5 or more fruits and vegetables per day; BP < 140/90 mmHg; regular exercise ≥ 150 min/week, and daily practice of CADRe program stress management techniques) was selected as the primary outcome measure since the main goal of this study is to assess the persistence of lifestyle change behaviors and risk factor control. The HHI, presented as a single score (range 0-7), will be assigned to

each subject yearly. Additionally, each of the 7 heart healthy characteristics will be assessed independently as a continuous variable.

Secondary Outcomes

Several additional outcomes will be assessed including:

- Changes in modifiable CVD risk factors: blood pressure, body composition and fitness, lipid levels and glucose
- Other biochemical markers: C-reactive protein
- Quality of Life: SF-36

Preliminary Findings:

Of the available 163 CADRe study subjects, 102 participants responded (63%) to study mailing: 80 meet eligibility criteria and agreed to make a study visit; 2 were ineligible; 17 declined screening interview / participation; 2 were undecided about participation, and; 1 deceased. Of the 80 eligible former CADRe study participants who agreed to make a study visit, 76 provided informed consent for at least one follow-up visit. Fifty-one participants provided at least one additional follow-up study visit. See Table 2 for actual longitudinal follow-up of study participants by cohort.

**Table 2. Actual Longitudinal Follow-Up of CADRe Study**

| | | | | Actual Visits | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cohort | # Pts Available | # Replied | # Enrolled | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Total Visits |
| 1 | 7 | 3 | 3 | | | | | 3 | 3 |
| 2 | 15 | 6 | 3 | | | | | 3 | 3 |
| 3 | 14 | 7 | 7 | | | | | 7 | 7 |
| 4 | 17 | 10 | 9 | | | | 6 | 8 | 14 |
| 5 | 12 | 8 | 7 | | | | 5 | 7 | 12 |
| 6 | 19 | 12 | 6 | | | | 4 | 6 | 10 |
| 7 | 15 | 9 | 5 | | | 4 | 3 | 4 | 11 |
| 8 | 12 | 6 | 4 | | | 4 | 4 | 4 | 12 |
| 9 | 9 | 5 | 5 | | | 4 | 4 | 2 | 10 |
| 10 | 10 | 9 | 9 | | 7 | 8 | 6 | 6 | 27 |
| 11 | 11 | 5 | 5 | | 5 | 5 | 4 | 3 | 17 |
| 12 | 10 | 3 | 3 | | 3 | 3 | 1 | 3 | 10 |
| 13 | 12 | 10 | 10 | 9 | 9 | 10 | 8 | 8 | 44 |
| Totals | 163 | 90 | 76 | 9 | 24 | 38 | 45 | 64 | 180 |

At study enrollment, participants were 66 yrs old (range 36 to 80), predominantly Caucasian male (79%) and significantly overweight with a BMI of 29.8; similar to their pre-CADRe study BMI of 29.1. Subjects were a mean of 3.2 yrs post CADRe Study completion or anticipated completion. Of the individual CADRe Study lifestyle components, participants were most compliant with exercise (goal ≥ 180 minutes/week): mean weekly time =183 minutes of moderate to vigorous physical activity. Although few participants reported a strict vegan dietary pattern following completion of the CADRe Study, dietary fiber and average fruit and vegetable intake was higher than the average U.S intake at 29 grams/day and 9.7 servings per day, respectively. Participants continued to have difficulty in performing 1 hour of stress management daily. Participants reported an average time of 154 minutes/week spent in any of the five CADRe Study techniques with only 33% reporting daily performance of at least 1 stress

management technique. Table 3 provides a preliminary descriptive analysis for the major outcome variables as an aggregate sample for the initial study visit. Individual HHI scores (composite score of heart healthy behaviors) has not yet been calculated, however, at least 5 of the 7 heart healthy behaviors are being met by the aggregate sample (LDL-cholesterol < 100 mg/dL; dietary fiber intake ≥ 25 gms/day; consumption of 5 or more fruits and vegetables per day; BP < 140/90 mmHg, and regular exercise ≥ 150 min/week).

**Table 3: Major Outcomes Variables at Initial Study Visit**

| Outcome Variable (n=76) | Mean | SD |
|---|---|---|
| Weight (kg) | 88.4 | 22.5 |
| Body Mass Index (BMI) | 29.8 | 6.3 |
| % Body Fat (n=74) | 31.2 | 9.8 |
| Systolic BP (mmHg) | 125.6 | 12.6 |
| Diastolic BP (mmHg) | 71.3 | 6.8 |
| Fasting Glucose (mg/dL) | 94.8 | 13.4 |
| Total Cholesterol (mg/dL) | 154.4 | 35.5 |
| HDL Cholesterol (mg/dL) | 50.2 | 11.4 |
| LDL Cholesterol (mg/dL) | 86.2 | 30.7 |
| Triglycerides (mg/dL) | 129.6 | 67.8 |
| C-Reactive Protein (mg/dL) (n=74)* | 0.197 | 0.365 |
| Daily Dietary Fiber (gms ) | 28.6 | 14.1 |
| Daily Fruit/Vegetable Servings | 9.7 | 5.5 |
| Weekly Exercise Time (minutes) | 183.0 | 167.0 |
| Weekly Stress Mgt Time (minutes) | 154.1 | 166.8 |
| Physical Composite Score | 44.2 | 11.5 |
| Mental Composite Score | 54.1 | 8.2 |

*Two outliers (C - reactive protein > 6.00) excluded from analysis

Preliminary analysis of changes in modifiable CVD risk factors (BP, body composition and fitness, lipid levels and glucose) can be assessed in comparison to the final CADRe Study visit (Table 4) in those subjects who have completed a 5-year follow-up study visit. In 62 participants with Year 5 data, there were significant increases in both body composition and systolic BP when compared to final CADRe study visit data. Body anthropometrics show an 8% mean weight gain and a 22% increase in body fat despite reporting a mean of 175 minutes per week of moderate physical activity. Systolic BP increased by 4%. No significant change was seen in diastolic BP, glucose, HDL or CRP. However, significant reductions in TC, LDL and TG at Year 5 were 4%, 4% and 10%, respectively. Of the 56 participants on lipid-lowering medications, 93% reported either no change (n=29) or an increase (n=23) in these medications which may account for the lipid profile changes.

**Table 4. Select Outcome Variables at 5-Year vs. Final CADRe Study Visit (n=62)**

| | Final CADRe Study Visit | 5-Yr Follow-up Visit | Change | P |
|---|---|---|---|---|
| **Body Composition/Blood Pressure (BP)** | | | | |
| Weight (kg) | 82.5 ± 22.6 | 89.2 ± 25.3 | 6.7 ± 9.9 | <0.001 |
| BMI (kg/m$^2$) | 27.6 ± 6.1 | 30.2 ± 6.7 | 2.6 ± 3.6 | <0.001 |
| % Body Fat* | 26.4 ± 9.1 | 31.2 ± 9.2 | 4.8 ± 4.3 | <0.001 |
| Systolic BP (mmHg) | 120.8 ± 12.4 | 125.4 ± 14.7 | 4.6 ± 14.2 | 0.014 |
| Diastolic BP (mmHg) | 69.1 ± 7.3 | 70.9 ± 7.7 | 1.8 ± 8.9 | 0.121 |
| **Laboratory (mg/dL)** | | | | |
| Glucose (mg/dL)** | 96.8 ± 15.7 | 96.2 ± 17.9 | -0.7 ± 16.5 | 0.746 |
| Total Cholesterol (mg/dL) | 158.9 ± 31.3 | 150.3 ± 30.1 | -8.6 ± 29.9 | 0.027 |
| LDL-Cholesterol(mg/dL) | 87.1 ± 23.2 | 81.5 ± 24.5 | -5.6 ± 21.6 | 0.046 |
| HDL-Cholesterol(mg/dL) | 46.1 ± 10.2 | 48.7 ± 13.1 | 2.6 ± 11.2 | 0.076 |
| Triglycerides (mg/dL) | 157.7 ± 88.8 | 130.0 ± 84.5 | -27.8 ± 75.5 | <0.001 |
| C-reactive protein (mg/dL)# | 0.226 ± 0.275 | 0.242 ± 0.412 | 0.016 ± 0.379 | 0.479 |

Values are mean ± SD; *n=57; **n=61; #n=60.

Adverse Events: There have been 2 adverse events (AEs) reported to the WRAMC HUC during this study:

- Patient underwent 3-vessel coronary artery bypass surgery & aortic valve replacement
- Patient underwent balloon angioplasty with placement of 2 stents.

**Task #4: Ongoing enrollment for "*B*etter Adherence *to T*herapeutic *L*ifestyle Change *E*fforts (BATTLE) Trial".**

**Status:** WRAMC HUC approved protocol on 25 April 2006. Final study approval from CIRO was granted on 28 April 2006. The MRMC Memorandum of Deferral was received 5 Jul 06. Change of PI to COL Randolph Modlin, Chief, WRAMC Cardiology, was approved 3 December 2008. Five approved study addendums have been previously reported. Addendum #6 (outlined below) was reviewed by WRAMC HUC on 13 Oct 2010 and revisions are pending. The annual Continuing Review was approved by WRAMC DCI HUC on 5 November 2010. This study is now closed to enrollment, data collection is complete (except proposed addendum) and final data reconciliation and analysis is in progress. Publication plan in progress. "Methods/Demographics" manuscript and "Integration of mindfulness into a support group curriculum" in progress.

Proposed Addendum #6:
During conduct of the support groups, participants offered many reasons for their success in making positive lifestyle changes. Conduct of a formative evaluation of the lifestyle change program is being proposed for the primary purpose of improving future lifestyle programs. The specific aims of this evaluation are to better understand subjects' experiences and recommendations regarding:
1) Decision to enroll in a lifestyle change program
2) Effectiveness of the lifestyle program
3) Suggestions for improving the lifestyle program, and;
4) Suggestions for maintaining positive lifestyle behaviors after program completion.

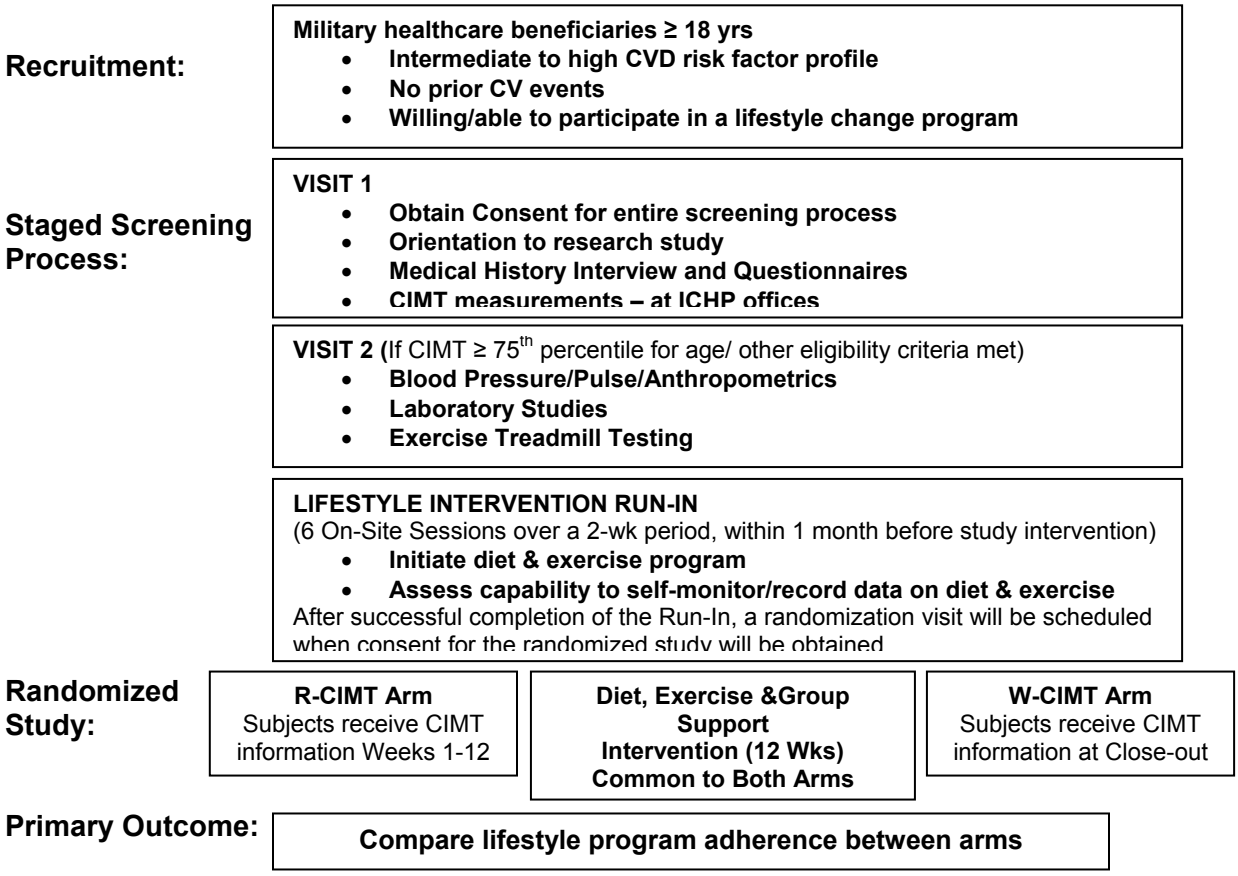
All randomized subjects (n=166) will be invited to complete a written follow-up survey that would quantify their personal experience and satisfaction with the lifestyle program. An investigator

developed 29-item purpose-designed survey will be used as no validated research instrument to meet specific evaluative needs is available. In addition to this survey, participants will also complete the diet and exercise questionnaires used in the original study and compared to study completion endpoints. A qualitative methodology using an evaluation approach will also be employed. Open-ended interviews will allow all participants, not just the study completers, to describe what was meaningful and salient for them, including their overall experience attempting to improve their diet and exercise habits, the perceived benefits and burdens, and suggestions for program improvement.

Study Design and Objectives

The purpose of this study is to determine whether knowledge of abnormal results from a noninvasive test for detection of subclinical atherosclerosis (CIMT), in addition to knowledge of CVD risk factors, enhances adherence to healthy lifestyle behaviors in comparison to only CVD risk factor knowledge. This two-arm, double-blinded study (see Figure 1) will randomize subjects to either receive CIMT results (R-CIMT Group) or have CIMT results withheld (W-CIMT Group) in the setting of a 3-month TLC intervention. After the 3-month TLC intervention period is completed, subjects who had CIMT results withheld will receive this information. Because knowledge of the study hypothesis could impact their behavior during the lifestyle intervention, subjects will be blinded to the study hypothesis. Similarly, research staff implementing the TLC intervention will be blinded to subjects' randomization assignment. Randomization assignment will also be blinded in the assessment of endpoints.

**Figure 1. BATTLE Trial Design**



Hypothesis

Subjects with CVD risk factors who have knowledge of their own CIMT test results showing significant subclinical atherosclerosis will demonstrate better adherence to TLC than those subjects from whom the CIMT test information is withheld.

Primary Outcome Measure

A composite index of adherence to the TLC intervention was selected as the primary outcome measure since the main goal of this study is to assess the impact of CIMT imaging knowledge on change in lifestyle behaviors. A combined measure of adherence, reflecting both aspects of the lifestyle intervention (Mediterranean-type diet, moderate aerobic exercise), was chosen that uses accepted measures of diet and exercise adherence reported in the literature. Although any of the modifiable CVD risk factors could have been selected as surrogate markers of adherence, factors aside from behavioral change could affect changes in these risk factors such as individual variability in response to the interventions or changes in pharmacologic therapy by the subjects own healthcare providers who are separate from the research staff. Also, not all subjects are expected to need improvement in the same CVD risk factor, thus, selection of a single risk factor as the primary outcome variable would be difficult and arbitrary. Use of a composite measure of risk factors, such as the Framingham Risk Score, is not validated for serial assessment in a short-term study.

Secondary Outcomes

Several additional outcomes will be assessed including:

- Adherence to each TLC Program component: Diet, Exercise, Attendance at weekly on-site sessions
- Changes in modifiable CVD risk factors: blood pressure, body composition and fitness, lipid levels, glucose/insulin resistance
- Other biochemical markers: C-reactive protein (CRP)
- Emotional factors: Anxiety Score, Stage of Change related to lifestyle behaviors, Self-efficacy, Motivation
- Atherosclerosis and CIMT Knowledge Assessment Score (only in CIMT-R subjects)

Study Population

The study will be conducted with individuals at moderate to high risk for cardiovascular events based on CVD risk factor profile and evidence of significant subclinical atherosclerosis. From our previous experience in recruiting military healthcare beneficiaries for a lifestyle intervention study, it is projected that one-third of the population screened will meet CIMT criteria > 75$^{th}$ percentile for age. Despite this high ratio of screened to eligible subjects, the presence of an abnormal scan is a crucial feature in the study design, which will specifically allow the motivational impact of CIMT imaging to be determined.

Preliminary Findings:

Since November 2007, 1068 patients have given permission for a study team member to contact them regarding this study. Approximately 41% of “interested” patients telephonically screened were eligible to initiate the study screening process. Over 48% of those contacted opted out (n=507) of the study primarily for time commitment and travel/distance reasons. The primary reason for ineligibility on the initial telephone screen was low cardiovascular risk profile. Of the 275 consented subjects who were considered screen failures, 60% screened out primarily by CIMT (<75 percentile for gender/age), 14% had an acceptable past medical history, 11% withdrew consent, 6% did not meet diagnostic or severity criteria, 1% had an intercurrent medical event and 8% were categorized as other (deployment, relocation, job conflicts). In

summary, approximately 18% of those patients who met initial screening criteria after the telephone screen (n=948) randomized into the main study. See Figure 1 for recruitment / enrollment flow diagram.

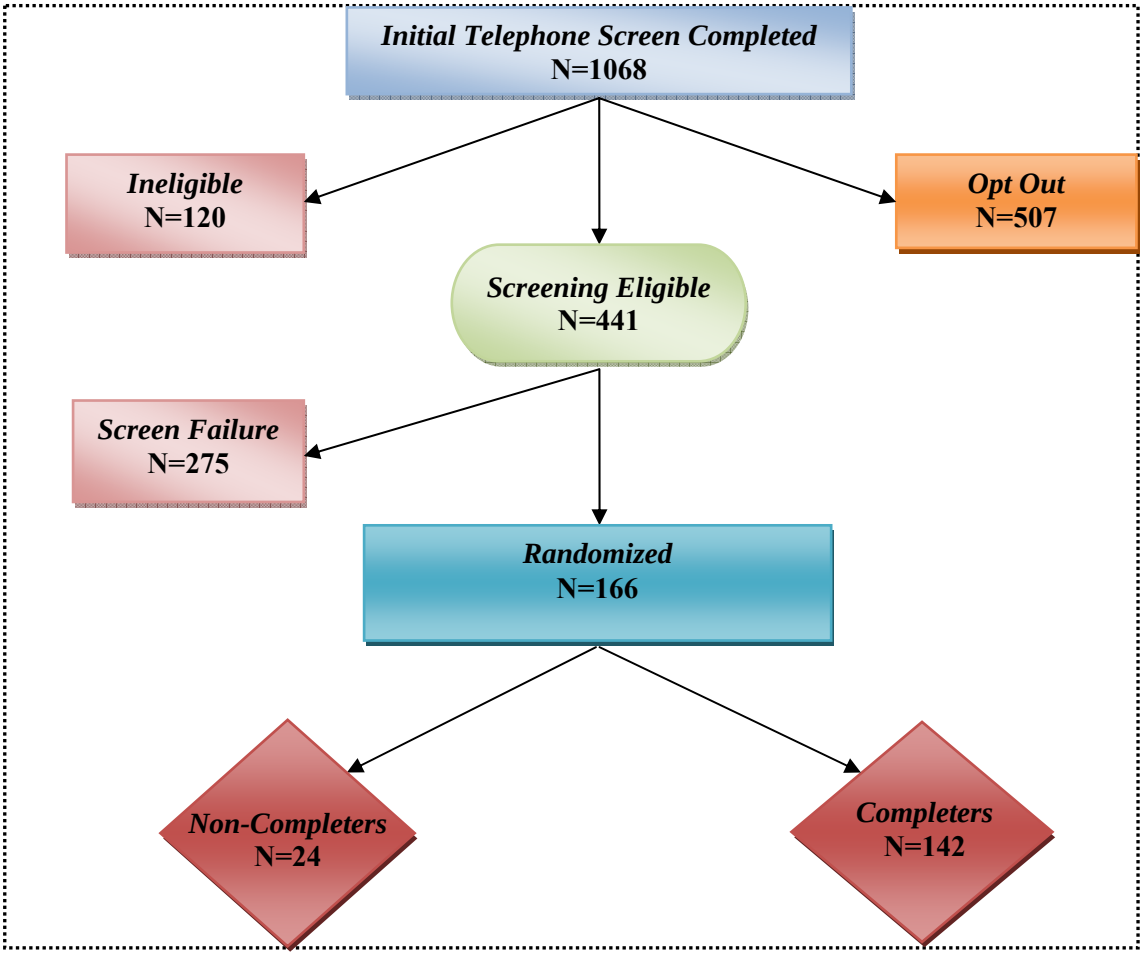



**Figure 2. BATTLE Study Flow Diagram for Screening & Enrollment of Subjects**

Thirty RI groups were conducted with 166 subjects successfully completing the RI phase and randomizing into the Main Study. Thirty Main Study Support Groups yielded 142 study completers and 24 non-completers (14.5% dropout rate). The final study support group was completed on 1 July 2010 and all closeout study visits were complete by mid July 2010. Of the 24 non-completers, 6 withdrew their consent after randomization, 5 were lost to follow-up, 3 could not complete the study due to a non-study related adverse event, 5 did not comply with the study protocol (lack of required data collection) and 5 left the study early for other reasons (lack of supervisor support, deployment and job relocation).

Although complete study data is being managed by PREMIER Research and study subject group assignment is not known the study research team, some preliminary analyses has been conducted on site.

In 166 randomized subjects, the mean age is 53.7 ± 10.8 with a range of 26 to 78 years old, 61% female, 56% were from minority groups and 12% have Type 2 diabetes. Of the randomized subjects, 24% were active duty, 36% were retired from the military services, and 40% were eligible family members. At baseline, randomized subjects were obese (BMI = 31.7 ± 5.5; weight

= 200 ± 40 lbs; % Body Fat = 37.2 ± 8.5) with 90% of subjects having a BMI ≥ 25 and 60% of those with BMI ≥ 30.

Table 5 depicts the change in select outcome variables to date between baseline and study completion in the 142 completer subjects. Preliminary data analysis on these completers, comparing study completion to baseline, was conducted using *t-test* statistics. Measures of obesity including weight and BMI declined 5% and percent of body fat was reduced by 5%. Additionally, a 5% reduction in waist circumference and a 7% reduction in abdominal sagittal diameter were seen. Serum glucose was reduced by 2%, triglycerides were lowered by 8% and fasting insulin was reduced by 12%. Levels of total cholesterol were reduced by 5%, LDL-cholesterol decreased by 7% and C-reactive protein (CRP) was decreased by 15%. Despite these positive changes, no significant difference was noted in HDL-cholesterol. Overall, this data further supports participation in a lifestyle modification program which includes education and frequent monitoring does result in substantial cardiovascular risk factor improvements. Some of these changes rival what has been observed with pharmacological treatment.

**Table 5. Select Outcome Variables in Study Completers (n=142)**

| | Baseline | Study Completion | Change | P |
|---|---|---|---|---|
| **Body Composition** | | | | |
| Weight (kg) | 90.5 ± 18.1 | 86.1 ± 17.3 | -4.5 ± 3.8 | <0.001 |
| BMI (kg/m$^2$) | 31.5 ± 5.6 | 29.9 ± 5.5 | -1.5 ± 1.3 | <0.001 |
| % Body Fat | 37.1 ± 8.5 | 35.3 ± 8.7 | -1.8 ± 2.6 | <0.001 |
| Sagittal Diameter (cm) | 24.0 ± 3.8 | 22.3 ± 3.7 | -1.7 ± 1.6 | <0.001 |
| Waist Circumference (cm) | 100.6 ± 13.1 | 95.6 ± 13.1 | -5.0 ± 4.1 | <0.001 |
| **Laboratory (mg/dL)** | | | | |
| Glucose (mg/dL) | 96.8 ± 19.0 | 93.1 ± 14.1 | -3.7 ± 14.6 | 0.003 |
| Insulin (uIU/mL) | 14.6 ± 12.6 | 11.2 ± 8.0 | -3.4 ± 7.6 | <0.001 |
| LDL-Cholesterol(mg/dL) | 119.5 ± 35.5 | 108.4 ± 28.8 | -11.2 ± 22.0 | <0.001 |
| HDL-Cholesterol(mg/dL) | 56.0 ± 15.9 | 55.4 ± 14.5 | -0.61 ± 7.7 | 0.348 |
| Triglycerides (mg/dL) | 122.2 ± 62.4 | 105.3 ± 52.6 | -16.9 ± 43.8 | <0.001 |
| C-reactive protein (mg/dL) | 0.425 ± 0.528 | 0.352 ± 0.461 | -0.074 ± 0.318 | 0.007 |

Values are mean ± SD.

Additionally, data analysis was conducted on a study subset. This analysis is summarized in Task #10.1.

Protocol Deviation: One protocol deviation was reported to the WRAMC DCI Human Use Committee during this study. During a support group session, several participants made comments which may have unblinded their group assignment to the support group facilitator. Assessment of the event revealed that bias was unlikely since all members of the group received the same information during the group session and that there was no change in the risk level for subjects as a result of this disclosure. It was determined that continued reinforcement of the study "rules of engagement" to participants would minimize further unblinding.

Adverse Events: Ten serious (SAEs) and 25 non-serious AEs have been reported to WRAMC DCI Human Use Committee. A summary of AEs follows:

| **Serious AEs** | **Relationship to Study Participation** |
|---|---|
| Left iliac wing fracture | Unrelated |
| Endometrial polyps | Unrelated |
| MVA w/subsequent hospital stay + right ankle internal fixation | Unrelated |
| Elective bilateral inguinal hernia repair | Unrelated |
| Hospitalization - r/o cerebral aneurysm | Unrelated |
| Malignant ovarian CA - TAH/BSO | Unrelated |
| Worsening right great toe pain (required follow-up report) | Probable |
| Left tibia fx; subsequent ORIF left tibia | Unrelated |
| Atrial flutter / cardioversion / hospitalization | Unrelated |
| Rigors/Hospitalization/Hep infection | Unrelated |

| **Non-Serious AEs** | **Relationship to Study Participation** |
|---|---|
| Right hip pain (possible piriformis syndrome) | Possible |
| Thyroid FNA | Unrelated |
| Hospitalization - HTN crisis | Unrelated |
| Elective surgery - rt foot 1st TMT fusion | Unrelated |
| Lt shoulder dislocation / Lt gluteal injury | Unrelated |
| Right stellate ganglion block / facial pain | Unrelated |
| Right foot tenderness post-trauma from telephone | Unrelated |
| Right knee pain | Probable |
| Four Omega-3 sample redraws (samples hemolyzed) | Unrelated |
| Epidermal cyst removal | Unrelated |
| Left sided arm / facial pain / numbness | Unrelated |
| Worsening knee pain & achilles tendonitis | Probable |
| Gallstones - elective lap cholecystectomy | Unrelated |
| Worsening right abdominal pain | Probable |
| Squeezing sensation in chest | Unrelated |
| Rt wrist fx r/t fall at home | Unrelated |
| Worsening Bilateral ankle pain | Probable |
| Excision right nares / left mid clavicle BCC | Unrelated |
| Left ankle pain/swelling post-fall | Unrelated |
| Worsening left knee pain | Possible |

**Task #5: Begin transition away from the traditional Dr. Dean Ornish Program for Reversing Heart Disease protocol.**

**Status:** Enrollment into the Dr. Dean Ornish Program is closed and all active participants have completed their participation in the study. Data analysis is ongoing.

Subject Enrollment and Demographics
This program is closed to enrollment and all active subjects have completed the program. Subject enrollment was 422 participants including 25 cohorts and 4 retreats. 339 participants graduated from the program and 83 participants discontinued participation (20% dropout rate).

Demographic characteristics of participants were: average age of 66.1 years, 53% are female, 33% are veterans or the spouse of a veteran, and 41% have diagnosed coronary heart disease.

Outcome Data

Participants in the Dr. Dean Ornish Program at Windber Medical Center achieved significant improvement in levels of virtually all of the measured coronary artery disease (CAD) risk factors over the initial 12-week period (Table 6A). Measures of obesity including weight and BMI declined ~7%, levels of total cholesterol were reduced by nearly 13%, blood pressure dropped ~9%, measures of physical fitness increased more than 26%, and levels of depression decreased approximately 47%. These data demonstrate that lifestyle change programs may be important for primary prevention in individuals with diagnosed CAD and those at increased risk of disease. Results from the end of the year examination are shown in Table 6B. Over the course of one year, weight and BMI decreased ~9%, diastolic blood pressure decreased ~7%, measures of physical fitness increased 25%, and levels of depression decreased nearly 50%.

**Task #6: Complete enrollment in Global Profiling of Gene/Protein Expression and Single Nucleotide Polymorphisms Associated with Coronary Heart Disease Reversal, Sub-Study for Subjects in the Dr. Dean Ornish Program protocol.**

**Status:** Enrollment to the global profiling study is closed and all active participants have completed their participation in the study. Enrollment in the sub-study was closed as of July 27, 2007. Data analysis is ongoing.

Subject Enrollment and Demographics

Subject enrollment was 374. There were 166 participants taking part in the lifestyle change program, 140 subjects serving as the control group, and 68 participants enrolled in the Sub-study. Demographic characteristics of the control group were: average age of 63.7 years, 51% were female, 29% were veterans or the spouse of a veteran, and 34% have diagnosed coronary heart disease.

**Data:**

Inflammation biomarker panel – Statistical analysis was performed on the biomarker panel. An abstract was submitted and accepted to the American Heart Association's Arteriosclerosis, Thrombosis and Vascular Biology 2010 Scientific Sessions. A poster presentation based on the following abstract was presented in April 2010 in San Francisco, CA.

**Intensive Lifestyle Modification for CAD Reversal Successfully Reduces Circulating Levels of Metabolic Hormones Insulin and Leptin**

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**Rationale:** Metabolic hormones regulate energy balance and metabolism and thus represent an important link between obesity and cardiovascular disease. Elevated circulating levels of insulin and leptin have been associated with various forms of CVD and may exert atherogenic effects through vascular inflammation and endothelial dysfunction. Therapeutic interventions involving lifestyle modification remain controversial because long-term effects on metabolic hormones have not been well studied.

**Methods:** Patients (n=76) participated in a prospective, nonrandomized, lifestyle change program designed to stabilize or reverse progression of CAD through dietary changes, exercise, stress management, and group support. Nonintervention controls (n=76) were matched to patients based on age, gender, and both CAD and diabetes status. Fasting blood samples were collected at baseline, three-month, and one-year examinations. Changes in insulin and leptin levels measured in duplicate by radioimmunoassay, as well as traditional CAD risk factors, were evaluated over the course of the program.
**Results:** The program was effective in producing significant improvement in traditional CAD risk factors such as body mass index (-9.9%, $p<0.01$ compared to controls), total cholesterol (-5.5%, $p<0.05$), physical fitness (+37.2%, $p<0.01$), and future risk for CAD (-7.9%, $p<0.01$). Participants showed a significant reduction in insulin (-18.4%, $p<0.01$ compared to controls) and leptin (-32.7%, $p<0.001$ compared to controls) levels from baseline to the one-year examination. In analyses stratified by gender, both men and women experienced similar significant reductions in insulin and leptin levels.
**Conclusions:** In *at risk* patients motivated to participate, an intensive lifestyle change program can effectively alter traditional CAD risk factors and produce dramatic reductions in plasma insulin and leptin levels. Lifestyle interventions that promote successful weight reduction may reduce risk for cardiovascular events in part by mediating the atherogenic effects of circulating metabolic hormones.

A summary of the results for insulin and leptin is presented below. Table 6 shows levels of insulin and leptin, as well as physiological measures, at baseline. Change over time in Ornish participants and controls for insulin, leptin, and physiological measures is presented in Tables 7 and 8. Table 9 shows medications known to affect plasma levels of insulin, leptin, and lipids. Table 10 shows the effects of medication use on plasma insulin, leptin, and lipid levels.

Considerable effort was devoted to tabulating the number of brand name medications tracked in our database for each Ornish patient, and to reviewing the effects of medications on plasma insulin and leptin levels. We also collected information on the degree to which leptin and insulin change with other therapeutic or lifestyle regimens.

**Table 6. Insulin, Leptin, and Physiological Measures at Baseline by Case/Control Status**

| Measure (n) | Controls | Participants | p Value* |
|---|---|---|---|
| Metabolic hormones | | | |
| Insulin (150) | 14.3 ± 7.1 | 18.1 ± 10.2 | 0.01† |
| Leptin (152) | 19.0 ± 17.2 | 23.5 ± 18.6 | 0.06† |
| Physiological measures | | | |
| Age (152) | 60.6 ± 7.6 | 60.6 ± 7.6 | 0.99 |
| BMI (152) | 28.5 ± 4.5 | 32.9 ± 7.2 | <0.01 |
| SBP (146) | 132 ± 16 | 136 ± 17 | 0.12† |
| DBP (146) | 78.6 ± 10.1 | 81.0 ± 10.1 | 0.24† |
| HDL (152) | 49.4 ± 13.0 | 45.5 ± 13.4 | 0.06 |
| LDL (142) | 108 ± 34 | 112 ± 39 | 0.59 |
| TCH (152) | 185 ± 43 | 195 ± 48 | 0.20 |
| TG (152) | 144 ± 98 | 176 ± 94 | <0.01 |
| EC (122) | 9.3 ± 2.9 | 6.6 ± 2.1 | <0.01 |
| Fram risk (124) | 6.8 ± 6.7 | 8.8 ± 7.7 | 0.16† |

Values are presented as mean ± SD. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TCH, total cholesterol; TG, triglycerides; EC, exercise capacity.

*Tested by 1-factor ANOVA by cohort type.
†Tested by a nonparametric Mann-Whitney U test because data was not normally distributed after LN transformation.

**Table 7. Changes in Insulin, Leptin, and Physiological Measures by Case/Control Status**

| | Controls (n=76) | | | | Participants (n=76) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Measure | Baseline | Week 12 | Week 52 | % Change | Baseline | Week 12 | Week 52 | % Change | Between Group Value* |
| Metabolic hormones[†] | | | | | | | | | |
| Insulin | 14.3 ± 7.1 | 14.9 ± 6.3 | 14.9 ± 6.8 | +4.0 | 18.1 ± 10. | 14.8 ± 7.1[‡] | 14.6 ± 7.8[§] | -19.2 | <0.01 |
| Leptin | 19.0 ± 17.2 | 16.5 ± 14.7 | 20.3 ± 16.8 | +6.6 | 23.5 ± 18. | 14.3 ± 11.1[§] | 15.8 ± 13.6[§] | -32.9 | <0.01 |
| Physiological measures[‖] | | | | | | | | | |
| BMI | 28.5 ± 4.5 | 28.3 ± 4.7 | 28.7 ± 4.8 | +0.9 | 32.9 ± 7.2 | 30.5 ± 6.6[§] | 29.8 ± 6.8[§] | -9.3 | <0.01 |
| SBP | 132 ± 16 | 126 ± 15[‡] | 125 ± 13[‡] | -5.3 | 136 ± 17 | 122 ± 14[§] | 127 ± 17[§] | -6.4 | 0.56 |
| DBP | 78.6 ± 10.1 | 77.1 ± 8.3 | 77.3 ± 9.3 | -1.5 | 81.0 ± 10. | 73.0 ± 9.0[§] | 75.5 ± 9.5[§] | -6.7 | 0.02 |
| HDL | 49.4 ± 13.0 | 52.0 ± 13.1 | 47.9 ± 13.3 | -3.0 | 45.5 ± 13. | 38.5 ± 9.5[§] | 43.1 ± 10.5[‡] | -5.2 | 0.50 |
| LDL | 108 ± 34 | 106 ± 35 | 108 ± 34 | -0.4 | 112 ± 39 | 98 ± 32[§] | 109 ± 33 | -2.8 | 0.54 |
| TCH | 185 ± 43 | 187 ± 46 | 185 ± 43 | -0.2 | 195 ± 48 | 170 ± 43[§] | 185 ± 44[‡] | -5.0 | 0.07 |
| TG | 144 ± 98 | 156 ± 138 | 146 ± 88 | +2.0 | 176 ± 94 | 163 ± 73 | 163 ± 93 | -7.2 | 0.21 |
| EC | 9.3 ± 2.9 | 9.5 ± 2.8 | 9.3 ± 2.7 | -0.6 | 6.6 ± 2.1 | 8.4 ± 2.2[§] | 9.0 ± 2.6[§] | +37.6 | <0.01 |
| Fram risk | 6.8 ± 6.7 | 6.3 ± 6.5 | 6.7 ± 7.0 | -2.2 | 8.8 ± 7.7 | 8.3 ± 7.7 | 8.5 ± 7.4 | -3.9 | 0.49 |

Values are presented as mean ± SD; % change = week 0-52. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TCH, total cholesterol; TG, triglycerides; EC, exercise capacity.

*From independent samples t-tests (two-tailed) of Baseline to Week 52 changes in intervention participants compared to controls.

[†]There was 1.3% missing data.

[‡]Significantly different from Baseline at $p<0.05$ based on repeated-measures ANOVA.

[§]Significantly different from Baseline at $p<0.001$ based on repeated-measures ANOVA.

[‖]There was <5.8% missing data.

**Table 8. Changes in Insulin, Leptin, and Selected Physiological Measures by Gender**

| | | Controls (n=76) | | | | Participants (n=76) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Measure | Gender | Baseline | Week 12 | Week 52 | % Change | Baseline | Week 12 | Week 52 | % Change | Between Group p Value* |
| Metabolic hormones[†] | | | | | | | | | | |
| Insulin | F | 13.3 ± 6.3 | 14.3 ± 6.4 | 14.1 ± 6.7 | +5.7 | 18.0 ± 8.6 | 15.3 ± 7.0 | 14.5 ± 7.8[‡] | -19.5 | <0.01 |
| | M | 15.4 ± 7.7 | 15.6 ± 6.3 | 15.7 ± 6.9 | +2.4 | 18.2 ± 11.8 | 14.3 ± 7.3[‡] | 14.8 ± 7.8[‡] | -18.9 | <0.05 |
| Leptin | F | 27.4 ± 19.7 | 23.8 ± 16.7 | 28.9 ± 17.5 | +5.6 | 32.1 ± 19.7 | 19.9 ± 10.6[§] | 21.4 ± 12.3[§] | -33.3 | <0.01 |
| | M | 10.2 ± 7.0 | 8.8 ± 6.0 | 11.2 ± 9.9 | +9.5 | 14.5 ± 12.1 | 8.4 ± 8.4[‡] | 9.9 ± 12.3[‡] | -32.0 | <0.01 |
| Physiological measures[‖] | | | | | | | | | | |
| BMI | F | 29.0 ± 5.0 | 29.0 ± 5.1 | 28.2 ± 5.5 | -0.8 | 33.5 ± 7.1 | 31.1 ± 6.5[§] | 30.3 ± 6.9[§] | -9.6 | <0.01 |
| | M | 27.9 ± 4.0 | 27.6 ± 4.2 | 28.2 ± 4.1 | +1.0 | 32.2 ± 7.3 | 29.8 ± 6.8[§] | 29.4 ± 6.7[§] | -8.9 | <0.01 |
| DBP | F | 80.6 ± 10.4 | 77.9 ± 8.8 | 79.1 ± 9.2 | -1.8 | 81.3 ± 7.2 | 72.6 ± 8.0[§] | 76.1 ± 8.6[‡] | -6.4 | 0.09 |
| | M | 76.2 ± 9.2 | 76.3 ± 7.7 | 75.3 ± 9.1 | -1.2 | 80.7 ± 12.7 | 73.4 ± 10.2[§] | 74.9 ± 10.6[‡] | -7.2 | 0.12 |
| TCH | F | 202 ± 42 | 206 ± 48 | 199 ± 43 | -1.4 | 209 ± 47 | 183 ± 40[§] | 198 ± 43 | -5.4 | 0.28 |
| | M | 168 ± 36 | 168 ± 35 | 170 ± 39 | +1.3 | 179 ± 45 | 156 ± 41[§] | 171 ± 40 | -4.4 | 0.11 |
| TG | F | 161 ± 100 | 184 ± 181 | 155 ± 82 | -3.5 | 174 ± 84 | 179 ± 82 | 183 ± 110 | +5.2 | 0.45 |
| | M | 126 ± 94 | 126 ± 58 | 137 ± 95 | +9.5 | 178 ± 105 | 146 ± 57 | 143 ± 65 | -19.9 | <0.01 |
| EC | F | 8.4 ± 2.9 | 8.7 ± 2.8 | 8.4 ± 2.6 | -0.3 | 6.5 ± 1.9 | 8.0 ± 1.8[§] | 8.7 ± 2.3[§] | +35.0 | <0.01 |
| | M | 10.5 ± 2.3 | 10.6 ± 2.3 | 10.4 ± 2.5 | -1.0 | 6.7 ± 2.4 | 8.9 ± 2.5[§] | 9.4 ± 2.9[§] | +40.7 | <0.01 |

Values are presented as mean ± SD; % change = week 0-52. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; TCH, total cholesterol; TG, triglycerides; EC, exercise capacity.

*From independent samples t-tests (two-tailed) of Baseline to Week 52 changes in intervention participants compared to controls.

†There was <3.2% missing data.

‡Significantly different from Baseline at $p<0.05$ based on repeated-measures ANOVA.

§Significantly different from Baseline at $p<0.001$ based on repeated-measures ANOVA.

‖There was <7.2% missing data.

**Table 9. Medications Affecting Plasma Levels of Insulin, Leptin, and Lipids**

| Medication Category (n)* | Insulin | Leptin | HDL | LDL | TCH | TG |
|---|---|---|---|---|---|---|
| ACE inhibitor (16) | ↑ | ↑† | | ↓ | ↓ | ↓ |
| Anticoagulant (4) | | | ↑ | | | |
| Beta blocker (15) | ↑ | ↓ | ↓ | ↓ | ↓ | |
| Calcium channel blocker (13) | ↑ | ↓ | ↑ | ↓ | ↓ | ↓ |
| Insulin medication (7) | ▲† | ↓ | | | | |
| Diuretic (14) | | ↑† | | ↑ | ↑ | |
| Lipid lowering medication (22) | | ↓† | ↑† | ▼† | ▼† | ▼† |
| Nitrate (4) | | | ↑† | ↓ | ↓ | |
| Oral antiglycemic (14) | ▲† | | | | | |

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TCH, total cholesterol; TG, triglycerides.

Key to medication effects: ▲ – increase, main effect; ↑ – increase, side effect; ▼ – decrease, main effect; ↓ – decrease, side effect.

*The number of brand name medications in each category is indicated in parentheses.

†Considered a primary medication category in Table 10.

**Table 10. Effects of Medication Changes on Insulin, Leptin, and Selected Physiological Measures**

| Measure | All Participants | | | Composite Medications* | | | Primary Medications† | | |
|---|---|---|---|---|---|---|---|---|---|
| | % Change in One Year (n) | | | % Change in One Year (n) | | | % Change in One Year (n) | | |
| | Controls | Participants | Between Group p Value‡ | Controls | Participants | Between Group p Value‡ | Controls | Participants | Between Group p Value‡ |
| Metabolic hormones | | | | | | | | | |
| Insulin | +4.0 (75) | -19.2‖ (75) | <0.01 | +3.3 (60) | -14.2§ (47) | <0.01 | +4.7 (72) | -16.9§ (69) | <0.01 |
| Leptin | +6.6 (76) | -32.9‖ (76) | <0.01 | +13.0 (43) | -32.1‖ (41) | <0.01 | +9.9 (47) | -34.5‖ (50) | <0.01 |
| Lipid measures | | | | | | | | | |
| HDL | -3.0 (76) | -5.2§ (76) | 0.50 | -2.1 (41) | -6.3§ (39) | 0.22 | -2.5 (49) | -6.1§ (58) | 0.28 |
| LDL | -0.4 (71) | -2.8 (71) | 0.54 | +5.6 (41) | -3.4 (37) | 0.03 | +4.2 (47) | -0.1 (57) | 0.26 |
| TCH | -0.2 (76) | -5.0§ (76) | 0.07 | +3.4 (43) | -5.3§ (40) | <0.01 | +3.1 (50) | -3.3 (61) | 0.02 |
| TG | +2.0 (76) | -7.2 (76) | 0.21 | +4.5 (47) | -2.9 (48) | 0.47 | +7.3 (50) | -4.9 (61) | 0.19 |

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TCH, total cholesterol; TG, triglycerides.

*Composite medication categories for all measures are shown in Table 9.

†Primary medication categories include: for insulin — insulin medications, oral antiglycemics; leptin — ACE inhibitors, diuretics, lipid lowering medications; HDL — lipid lowering medications, nitrates; LDL — lipid lowering medications; TCH — lipid lowering medications; TG — lipid lowering medications.

‡From independent samples t-tests (two-tailed) of Baseline to Week 52 changes in intervention participants compared to controls.

§Significantly different from Baseline at p<0.05 based on repeated-measures ANOVA.

‖Significantly different from Baseline at p<0.001 based on repeated-measures ANOVA.

Based on these results, we have been able to show that the metabolic hormones insulin and leptin decrease significantly in patients involved in the lifestyle modification program compared to controls. There do not appear to be significant differences between males and females in regard to insulin/leptin lowering response following intervention. Likewise, changes in medication use and/or dosage during the program did not have significant effects on insulin and leptin response.

The Ornish program compares favorably with other lifestyle interventions for reducing circulating insulin and leptin levels (Table 11). A manuscript is in preparation based on this data, which we hope to submit to Nutrition, Metabolism, and Cardiovascular Diseases during the upcoming quarter. A manuscript is in preparation based on this data.

**Table 11. Change in insulin and leptin during various lifestyle interventions.**

| Variable | Units | Intervention | Mean follow-up¶ (weeks) | Baseline value ± SD | Mean change (%) | Reference |
|---|---|---|---|---|---|---|
| **Insulin** | pmol/L | exercise | 104 | 41.3 ± 1.2 | +17.7 | 13 |
| | mU/L | exercise | 96 | 13.4 ± 2.3 | +16.4 | 56 |
| | $pmol/L^{-1}$ | exercise | 8 | 80.8 ± 40.7 | +13.9 | 74 |
| | µU/mL | diet | 8 | 12.4 | +8 | 35 |
| | pmol/L | diet and exercise | 104 | 45 ± 14 | +6.7 | 12 |
| | pmol/L | lifestyle | 8 | 61 ± 32 | +6.5 | 23 |
| | mU/L | lifestyle | 24 | 11.9 | +4 | 11 |
| | mmol/L | exercise | 52 | 62.6 ± 53.6 | +2.6 | 48 |
| | pmol/L | lifestyle | 52 | 141 ± 105 ** | +2.5 | 73 |
| | IU/L | exercise | 12 | 9.26 ± 5.82 | +1.9 | 49 |
| | $pmol/L^{-1}$ | exercise | 16 | 92.3 ± 50.1 | -2.4 | 63 |
| | µU/mL | exercise | 1 | 16 ± 2 | -6.3 | 52 |
| | µU/mL | exercise | 24 | 24.57 ± 3.85 | -6.7 | 61 |
| | U/mL | diet | 12 | 18 ± 6 | -7.8 | 34 |
| | pmol/L | diet | 52 | 56.5 ± 3.96 | -8 | 3 |
| | pmol/L | lifestyle | 8 | 49 ± 21 | -8 | 23 |
| | µU/mL | exercise | 12 | 20.1 ± 3.5 | -9.5 | 77 |
| | µU/mL | diet | 20 | 4.82 | -10.6 | 9 |
| | IU/L | exercise | 24 | 12.3 ± 8.0 | -10.6 | 60 |
| | mU/L | diet (cod) | 8 | 10.1 ± 4.1 | -12 | 28 |
| | µU/mL | diet | 4 | 14.2 ± 5.8 | -12.7 | 33 |
| | µU/mL | diet and exercise | 12 | 16.7 ± 1.5 | -13.8 | 47 |
| | pmol/L | diet and exercise | 52 | 143 ± 82 | -14 | 29 |
| | µU/mL | diet and exercise | 24 | 25 ± 1 | -14 | 81 |
| | µU/mL | exercise | 12 | 9.7 ± 0.8 | -14.4 | 36 |
| | µU/mL | diet | 8 | 10.06 | -14.5 | 22 |
| | µU/mL | exercise | 52 | 13.8 ± 6.8 | -15 | 59 |
| | µU/mL | exercise | 12 | 21.8 ± 2.7 | -16.5 | 82 |
| | $µU/mL^{-1}$ | diet and exercise | 12 | 21 ± 2.7 | -16.7 | 46 |
| | pmol/L | supplement + exercise | 24 | 46 ± 11 | -17.4 | 80 |
| | µU/mL | lifestyle | 52 | 19.4 ± 10 | -17.5 | 17 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | µU/mL | exercise | 52 | 11.6 ± 4.9 | -18 | 27 |
| | pmol/L | diet and exercise | 52 | 81.3 ± 6.85 ** | -18.5 | 65 |
| | µU/mL | diet and exercise | 68 | 4.7 ± 0.4 | -19 | 14 |
| » | **µU/mL** | **Ornish Program** | **52** | **18.1 ± 10.2** | **-19.2** | |
| | µU/mL | diet | 13 | 10 | -20 | 15 |
| | IU/L | exercise | 12 | 13.8 ± 7.8 | -21 | 53 |
| | µU/mL | diet and exercise | 48 | 9.6 ± 7.9 | -21.9 | 41 |
| | mU/L | diet (salmon) | 8 | 10.8 ± 5.2 | -22 | 28 |
| | pmol/L | exercise | 24 | 102 ± 9 | -22.5 | 54 |
| | µU/mL | diet and exercise | 1 | 16.8 ± 1.5 | -22.6 | 71 |
| | pmol/L | exercise | 12 | 96.5 ± 49.5 | -22.9 | 70 |
| | IU/mL | lifestyle | 12 | 8.2 ± 7.0 | -23.2 | 76 |
| | mU/L | diet (fish oil) | 8 | 10.1 ± 4.6 | -23.7 | 28 |
| | pmol/L | exercise | 16 | 59 | -23.7 | 57 |
| | µU/mL | diet and exercise | 20 | 11.7 ± 8.4 | -24.8 | 62 |
| | pmol/L | diet | 12 | 54.4 ± 33.1 | -26.4 | 19 |
| | µU/mL | diet and exercise | 12 | 6.3 ± 4.9 | -27 | 5 |
| | µU/mL | exercise | 16 | 10.3 ± 10.4 | -27.2 | 55 |
| | µU/mL | exercise | 16 | 10.3 ± 10.4 | -27.2 | 78 |
| | µU/mL | diet | 8 | 11.94 | -27.5 | 22 |
| | µU/mL | diet and exercise | 4 | 12.8 ± 6.5 | -28.1 | 18 |
| | mU/L | yoga | 6.4 | 31.47 ± 17.28 | -29 | 1 |
| | µU/mL | diet and exercise | 3 | 33.8 ± 4.0 | -29.6 | 6 |
| | µU/mL | diet and exercise | 3 | 30.9 ± 3.3 | -30 | 7 |
| | mU/L | exercise and diet* | 8 | 7.3 ± 0.8 | -30 | 20 |
| | µU/mL | diet and exercise | 8 | 13.55 ± 13.35 | -30 | 64 |
| | mU/L | diet and exercise | 20 | 16.0 ± 8.0 | -30.1 | 45 |
| | µU/mL | diet and exercise | 16 | 18.1 | -30.9 | 67 |
| | µU/mL | diet | 20 | 19.0 ± 12.4 | -31 | 16 |
| | mU/L | lifestyle | 52 | 16 | -31 | 25 |
| | $\mu U/mL^{-1}$ | exercise | 15 | 19.4 ± 3.4 | -31 | 51 |
| | IU/mL | diet and exercise | 12 | 13.2 ± 6.6 | -31.8 | 68 |
| | pmol/L | diet | 4 | 8.1 ± 3.3 | -32 | 30 |
| | µU/mL | diet | 104 | 11.0 ± 5.0 | -36 | 8 |
| | µU/mL | lifestyle | 104 | 14 ± 4 | -36 | 10 |
| | $mU/mL^{-1}$ | exercise | 36 | 29.2 | -36.6 | 50 |
| | uk | diet | 8 | 23.7 ± 12.4 | -37 | 4 |
| | µU/mL | exercise | 12 | 11.5 ± 8.4 | -39 | 31 |
| | µU/mL | diet | 6 | 12.7 ± 10.1 | -39 | 39 |
| | IU/L | lifestyle | 9 | 10.12 ± 3.40 | -40.5 | 72 |
| | pmol/L | exercise | 12 | 109.0 ± 68.2 | -42.4 | 66 |
| | µU/mL | exercise | 12 | 8.47 ± 1.27 | -43.8 | 69 |
| | µU/mL | lifestyle | 24 | 45 ± 6.3 | -46.4 | 58 |
| | pmol/L | diet | 12 | 186 ± 65 | -49 | 2 |

| Variable | Units | Intervention | Mean follow-up (weeks) | Baseline value ± SD | Mean change (%) | Ref |
|---|---|---|---|---|---|---|
| **Leptin** | ng/ml | lifestyle | 52 | 18.4 ± 14.3 | +27.2 | 17 |
| | µg/l | exercise | 24 months | 7.4 ± 3.8 | +6.7 | 56 |
| | ng/ml | exercise | 16 | 10.6 ± 5.3 | 0 | 55 |
| | ng/ml | exercise | 1 | 21.5 ± 4.5 | -5.6 | 52 |
| | ng/ml | diet | 8 | 30.5 ± 16.3 | -9 | 35 |
| | ng/ml | exercise | 8 | 52.0 ± 14.4 | -9 | 43 |
| | mmol/L | lifestyle | 52 | 675 | -10.8 | 32 |
| | ng/ml | diet and exercise | 12 | 12.20 ± 3.22 | -11 | 42 |
| | $ng/mL^{-1}$ | exercise | 15 | 34.8 ± 5.8 | -12 | 51 |
| | ng/ml | diet | 12 | 9.6 ± 12.8 | -12.5 | 26 |
| | ng/ml | exercise | 9 | 8.15 ± 3.75 | -14 | 44 |
| | ng/ml | diet | 12 | 156.9 ± 84 | -17 | 21 |
| | ng/ml | diet and exercise | 12 | 15.1 ± 1.2 | -17 | 47 |
| | ng/ml | diet | 8 | 24.1 | -19.9 | 22 |
| | ng/ml | diet | 12 | 149.5 ± 84 | -23 | 21 |
| | ng/ml | lifestyle | 52 | 19.6 | -23.5 | 25 |
| | ng/ml | exercise | 52 | 6.7 ± 4.0 | -23.9 | 27 |
| | ng/ml | diet and exercise | 52 | 9.1 ± 6.2 | -24.2 | 40 |
| | U/L | diet and exercise | 52 | 33.5 ± 11.3 | -26 | 37 |
| | ng/ml | diet and exercise | 48 | 63.6 ± 27.0 | -27.8 | 41 |
| | ng/ml | diet and exercise | 4 | 7.8 ± 4.4 | -29.1 | 18 |
| » | **ng/ml** | **Ornish Program** | **52** | **23.5 ± 18.6** | **-32.9** | |
| | pg/mL | diet | 166.4 | 989 | -33.5 | 24 |
| | ng/ml | exercise and diet* | 8 | 28.3 ± 3.5 | -34 | 20 |
| | ng/ml | diet (cod) | 8 | 26.4 ± 18.7 | -34 | 28 |
| | ng/ml | diet (salmon) | 8 | 25.6 ± 19.5 | -35 | 28 |
| | µmol/L | lifestyle | 8 | 45.5 ± 26.2 | -35.4 | 23 |
| | ng/ml | diet (fish oil) | 8 | 28.6 ± 19.3 | -37 | 28 |
| | ng/ml | diet | 8 | 27.5 | -37.5 | 22 |
| | µmol/L | lifestyle | 8 | 10.3 ± 5.9 | -37.9 | 23 |
| | ng/ml | diet and exercise | 12 | 20.4 ± 4.5 | -38.2 | 38 |
| | ng/ml | diet and exercise | 12 | 24 ± 7 | -38.8 | 75 |
| | ng/ml | diet and exercise | 12 | 14.7 ± 5.3 | -39.4 | 5 |
| | ng/ml | diet | 6 | 36.5 ± 25.4 | -49.9 | 39 |
| | µg/ml | diet | 12 | 18.6 ± 11.9 | -52.2 | 19 |
| | ng/ml | diet and exercise | 12 | 7.2 | -53 | 79 |
| | ng/ml | diet | 4 | 33.1 ± 10.2 | -67.7 | 30 |

uk - unknown

*Supplement added to intervention

Inclusion criteria - studies conducted in 2007 or earlier, fasting insulin levels, intervention ≥1week, Baseline measures reported, studies reported in English, studies indexed in PubMed and available

**Separate data for men and women were combined and averaged to get mean % change

[¶]Follow up times are approximate and based on 4 weeks per month and 52 weeks per year

»Our data

Macrophage migration inhibitory factor (MIF) – MIF is an inflammatory cytokine that regulates smooth muscle cell migration and proliferation, and thus plays an important role in promoting development of atherosclerotic lesions. MIF has been shown to be an important biomarker for diseases with inflammation, such as CVD, diabetes, obesity, and cancer. Results of the statistical analysis show that MIF levels decreased significantly ($p<0.05$) in Ornish participants compared to controls at 12 weeks, but there was no difference in MIF levels between cases and controls at one year (Table 12A).

**Table 12A. Change in MIF levels in Ornish participants and controls at 12 weeks and 1-Yr.**

| Variable | Cohort Type | n | Baseline | Week 12 | % Change B to 12 Wk | Year 1 | % Change B to 1 Yr | Between Group B to W12 P Value | Between Group B to Y1 P Value |
|---|---|---|---|---|---|---|---|---|---|
| MIF | Control | 85 | 2.9±1.9 | 3.1±2.2 | +6.3% | 2.9±1.9 | +1.9% | 0.014 | 0.939 |
| | Ornish | 85 | 2.9±1.9 | 2.6±1.8 | -12.6% | 2.9±2.1 | +1.3% | | |

Stratification by gender (Table 12B) indicated that only women who participated in the Ornish program showed significant reductions in MIF levels at 12 weeks (-23%). Men who participated in the program showed minimal change in MIF at 12 weeks (-2.3%).

**Table 12B. Change in MIF levels in Ornish participants and controls stratified by gender at 12 weeks and 1-Yr.**

| Variable | | Cohort Type | n | Baseline | Week 12 | % Change B to 12 Wk | Year 1 | % Change B to 1 Yr | Between Group B to W12 P Value | Between Group B to Y1 P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| MIF | F | Control | 40 | 3.3±2.1 | 3.7±2.6 | +12.7% | 3.2±2.2 | -3.7% | 0.001 | 0.722 |
| | | Ornish | 40 | 3.1±1.9 | 2.4±1.6[b] | -23.0%[b] | 3.1±2.2 | -0.4% | | |
| | M | Control | 45 | 2.5±1.7 | 2.5±1.5 | -1.2% | 2.7±1.7 | +8.5% | 0.907 | 0.680 |
| | | Ornish | 45 | 2.8±1.9 | 2.7±2.0 | -2.3% | 2.9±2.0 | +2.9% | | |

Gene Expression – We have finalized two data sets consisting of: (1) 63 Ornish participants and 63 matched controls with gene expression data at all three time points, and (2) 89 Ornish participants (matched and unmatched) with gene expression data at all three time points. Statistical analysis was completed on the first gene expression data set.

The gene expression datasets (456 arrays assaying ~18,000 genes each) likely represent the largest gene expression datasets on participants in a CVD lifestyle change program.

Integrity of the microarray gene expression data in the first data set was assessed by rigorous QC. CEL files from all participants and controls were imported into Partek® Genomics Suite v6.5 (Partek Incorporated, St. Louis, MO). Probe set intensities were obtained by Robust Multichip Algorithm (RMA) background correction, quantile normalization, median polish summarization, and $\log_2$ transformation. To assess data integrity, the processed intensity data was subjected to standard GeneChip® quality control parameters, which evaluated assay performance and ensured suitability for analysis. All arrays passed the quality control assessment and thus were included in further analyses.

Duplicate blood samples were collected from seven randomly-selected participants at each time point and applied to U133A 2.0 arrays as outlined above to evaluate the consistency of gene expression among duplicate assays. Overall repeatability of the array data was first assessed using Pearson correlation coefficients between all pair-wise comparisons of RMA normalized intensities. The average correlation between the 21 duplicate samples was 0.992 $\pm$ 0.006, range 0.969—0.996), indicating high repeatability of the microarray data. Paired t-tests were then used to identify genes that consistently showed significant differences in expression among the duplicate samples as a filter for exclusion. Comparative analysis identified nine genes that were differentially expressed based on a false discovery rate (FDR) adjusted p-value <0.05 between the duplicate samples and thus were excluded from further analysis: CKLF-like MARVEL transmembrane domain containing 6 (CMTM6); dehydrogenase/reductase (SDR family) member 9 (DHRS9); guanine nucleotide binding protein (G protein), 11 (GNA11); kelch-like 18 (KLHL18); kinesin family member 1A (KIF1A); mitogen-activated protein kinase 1 interacting protein 1-like (MAPK1IP1L); nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor) (NR3C1); transportin 1 (TNPO1); vesicle-associated membrane protein 1 (synaptobrevin 1) (VAMP1).

Differential gene expression analysis between time points (baseline—12 weeks, baseline—52 weeks) was conducted using ANOVA with participant as the random effects factor and time point as the fixed effects factor. Resulting p-values were adjusted by FDR correction for multiple testing. Stringent gene lists were generated through combined significance (FDR-adjusted $p<0.05$) and expression change ($\geq$1.1-fold) filtering. For matched controls, gene lists were filtered at FDR-adjusted p-value <0.05 with no fold change filter, because our objective was to identify any differentially expressed genes with greater statistical certainty to serve as a comparison for gene expression changes in the cardiovascular intervention participants.

Functional enrichment analysis was performed on the stringent gene lists using Gene Ontology (GO) annotations to summarize the most enriched biological processes. The GO annotations were ranked by an enrichment p-value, which identified biological processes represented more frequently than expected by chance among genes that changed significantly in expression during the Ornish program.

Significant changes in expression were observed as follows:

1. Changes in expression $\geq$1.1-fold at a False Discovery Rate (FDR) $p<0.05$
    - -- Lifestyle participants
        - 26 genes at 3 months
        - 162 genes at one year
    - -- Controls
        - 0 genes at 3 months
        - 23 genes at one year

2. Changes in expression ≥1.2-fold at a False Discovery Rate (FDR) $p<0.05$

-- Lifestyle participants

20 genes at 3 months

33 genes at one year

-- Controls

0 genes at 3 months

0 genes at one year

Many genes were involved in immune and defense response. However, other biological processes such as cell adhesion/migration and carbohydrate/cholesterol metabolism also were altered. Many genes altered at 3 months remained altered at one year. This is the first study to show that lifestyle change programs can produce fundamental molecular changes that persist up to one year (Tables 13 and 14).

When participants were stratified by gender, different patterns of expression were evident between men and women. Significant changes in expression (Table 15) indicated a clear gender difference in the timing of molecular response:

-- Men

12 genes at 3 months

0 genes at one year

-- Women

0 genes at 3 months

19 genes at one year

In the coming year, validation qRT-PCR experiments will be performed to confirm differential gene expression detected by microarray analysis. Total RNA (500 ng) will be reverse-transcribed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Carlsbad, CA). Resulting cDNA (10 ng) will be subjected to qRT-PCR using TaqMan® Gene Expression Assays (Applied Biosystems) according to the manufacturer's protocol on an iCycler iQ™ Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA). All samples will be run in duplicate for each assay and the mean value of the duplicate assays was analyzed by the $\Delta\Delta C_T$ method, which determines levels of expression for each target gene at each time point.

**Table 13. Genes showing ≥1.25-fold change in expression from baseline to three-months in Ornish program participants**

| Probe ID | Gene Name | Symbol | Fold Change | GO Biological Process[a] |
|---|---|---|---|---|
| 202018_s_at | Lactotransferrin | LTF | –1.86 | Immune response, ion transport, iron homeostasis |
| 206676_at | Carcinoembryonic antigen-related CAM8 | CEACAM8 | –1.68 | Immune response |
| 212531_at | Lipocalin 2 | LCN2 | –1.55 | Transporter activity; binding[b] |
| 207269_at | Defensin α4, corticostatin | DEFA4 | –1.53 | Defense response |
| 205033_s_at | Defensin α1,α1B,α3, neutrophil-specific | DEFA1,1B,A3 | –1.49 | Immune response, defense response, chemotaxis |
| 212768_s_at | Olfactomedin 4 | OLFM4 | –1.49 | Cell adhesion, protein binding |
| 207802_at | Cysteine-rich secretory protein 3 | CRISP3 | –1.45 | Immune response, defense response |
| 210244_at | Cathelicidin antimicrobial peptide | CAMP | –1.35 | Defense response |
| 203757_s_at | Carcinoembryonic antigen-related CAM6 | CEACAM6 | –1.33 | Signal transduction, cell-cell signaling |
| 207329_at | Matrix metallopeptidase 8 | MMP8 | –1.30 | Ossification, proteolysis, metabolism, collagen catabolism |
| 205557_at | Bactericidal/permeability-increasing protein | BPI | –1.29 | Immune response, (-) regulation of IL6, IL8; lipid binding[b] |
| 208470_s_at | Haptoglobin/haptoglobin-related protein | HP/HPR | –1.28 | Defense response, proteolysis, iron homeostasis |
| 206871_at | Elastase, neutrophil expressed | ELANE | –1.26 | Proteolysis, inflammatory response, immune response |
| 205513_at | Transcobalamin I (vit B12 binding protein) | TCN1 | –1.25 | Cobalt ion transport, cobalamin (vitamin B12) transport |
| 206851_at | Ribonuclease, RNase A family 3 | RNASE3 | –1.25 | RNA catabolism, defense response |
| 203153_at | Interferon-induced protein with TPRs 1 | IFIT1 | +1.27 | Binding[b] |

Abbreviations: CAM, cell adhesion molecule; TPR, tetratricopeptide repeat; GO, Gene Ontology.
CEACAM6 was represented by multiple probes.
[a]Derived from NetAffx™ Analysis Center (http://www.affymetrix.com/analysis/index.affx).
[b]GO molecular function.

**Table 14. Genes showing ≥1.25-fold change in expression from baseline to one year in Ornish program participants**

| Probe ID | Gene Name | Symbol | Fold Change | GO Biological Process[a] |
|---|---|---|---|---|
| 202018_s_at | Lactotransferrin* | LTF | –1.67 | Immune response, ion transport, iron homeostasis |
| 221748_s_at | Tensin 1 | TNS1 | –1.55 | Cell migration, cell-substrate junction assembly |
| 212531_at | Lipocalin 2* | LCN2 | –1.47 | Transporter activity; binding[b] |
| 206676_at | Carcinoembryonic antigen-related CAM8* | CEACAM8 | –1.44 | Immune response |
| 214407_x_at | Glycophorin B (MNS blood group) | GYPB | –1.41 | Signal transduction; receptor activity[b] |
| 206698_at | X-linked Kx blood group | XK | –1.41 | Amino acid transport |
| 206665_s_at | BCL2-like 1 | BCL2L1 | –1.39 | Response to hypoxia, apoptosis, response to oxidative stress |
| 203502_at | 2,3-bisphosphoglycerate mutase | BPGM | –1.37 | Carbohydrate metabolism, glycolysis, respiration |
| 203115_at | Ferrochelatase | FECH | –1.35 | Metabolites/energy, porphyrin/heme synthesis, cholesterol metabolism |
| 207802_at | Cysteine-rich secretory protein 3* | CRISP3 | –1.32 | Defense response, immune response |
| 208470_s_at | Haptoglobin/haptoglobin-related protein* | HP/HPR | –1.30 | Defense response, proteolysis, iron homeostasis |
| 212768_s_at | Olfactomedin 4* | OLFM4 | –1.29 | Cell adhesion, protein binding |
| 213446_s_at | IQ motif containing GTPase activating pr 1 | IQGAP1 | –1.28 | Small GTPase-mediated signal transduction |
| 208632_at | Ring finger protein 10 | RNF10 | –1.28 | Transcription, (-) Schwann cell proliferation, (+) myelination |
| 221627_at | Tripartite motif-containing 10 | TRIM10 | –1.28 | Erythrocyte differentiation; protein binding, metal ion binding[b] |
| 218418_s_at | KN motif and ankyrin repeat domains 2 | KANK2 | –1.28 | — |
| 217878_s_at | Cell division cycle 27 homolog | CDC27 | –1.27 | Mitotic metaphase/anaphase transition, cell proliferation, cell division |
| 210244_at | Cathelicidin antimicrobial peptide* | CAMP | –1.27 | Defense response |
| 200615_s_at | Adaptor-related protein complex 2, β1 | AP2B1 | –1.26 | Protein transport, defense response |
| 205557_at | Bactericidal/permeability-increasing protein* | BPI | –1.25 | Immune response, (-) regulation of IL6, IL8; lipid binding[b] |
| 211993_at | WNK lysine deficient protein kinase 1 | WNK1 | –1.25 | (+) regulation of blood pressure, protein phosphorylation, ion transport |
| 216050_at | — | — | +1.48 | — |

Abbreviations: CAM, cell adhesion molecule; GO, Gene Ontology.
TNS1, FECH, GYPB, and HP were represented by multiple probes.
[a]Derived from NetAffx™ Analysis Center (http://www.affymetrix.com/analysis/index.affx).

[b]GO molecular function.

**Table 15. Genes showing ≥1.2-fold change in expression during the lifestyle intervention in participants stratified by gender**

| Probe ID | Gene Name | Symbol | Fold Change | GO Biological Process[a] |
|---|---|---|---|---|
| **Men – Baseline to 3 months** | | | | |
| 202018_s_at | Lactotransferrin* | LTF | –1.94 | Immune response, ion transport, iron homeostasis |
| 206676_at | Carcinoembryonic antigen-related CAM8* | CEACAM8 | –1.80 | Immune response |
| 212768_s_at | Olfactomedin 4* | OLFM4 | –1.68 | Cell adhesion, protein binding |
| 207802_at | Cysteine-rich secretory protein 3* | CRISP3 | –1.57 | Defense response, immune response |
| 210244_at | Cathelicidin antimicrobial peptide* | CAMP | –1.39 | Defense response |
| 207329_at | Matrix metallopeptidase 8 | MMP8 | –1.33 | Ossification, proteolysis, metabolism, collagen catabolism |
| 220570_at | Resistin* | RETN | –1.30 | Response to insulin, fat cell differentiation |
| 209771_x_at | CD24 molecule | CD24 | –1.28 | Inflammatory response, immune response, cell-cell adhesion |
| 211113_s_at | ATP-binding cassette, sub-family G | ABCG1 | +1.21 | Lipid transport, cholesterol/lipid storage, lipoprotein remodeling |
| 203505_at | ATP-binding cassette, sub-family A | ABCA1 | +1.27 | Lipid metabolism, cholesterol metabolism/transport/storage |
| **Women – Baseline to 1 year** | | | | |
| 202018_s_at | Lactotransferrin* | LTF | –1.57 | Immune response, ion transport, iron homeostasis |
| 217878_s_at | Cell division cycle 27 homolog | CDC27 | –1.35 | Cell proliferation, cell division |
| 200615_s_at | Adaptor-related protein complex 2, β1 | AP2B1 | –1.32 | Protein transport, defense response |
| 213926_s_at | ArfGAP with FG repeats 1 | AGFG1 | –1.21 | Cell differentiation, organism development, transport |
| 203609_s_at | Aldehyde dehydrogenase 5 family, A1 | ALDH5A1 | –1.20 | Glucose/glycerophospholipid/fatty acid metabolism |

Abbreviations: CAM, cell adhesion molecule; GO, Gene Ontology; [a]Derived from NetAffx™ Analysis Center; [b]GO molecular function.

Plasma Metabolites – We continued our collaboration with Dr. Dean Jones and Dr. Quinlyn Soltow at Emory University to profile plasma metabolites associated with CVD development. During the year, we analyzed a total of 17 Ornish patients and 17 matched controls (all at three time points) by liquid chromatography-Fourier transform mass spectrometry (LC-FTMS). All assays were run in duplicate.

Metabolomic profiling identified 12,859 metabolite features in plasma; 4,432 features were present in more than 90% of the 102 samples analyzed. False discovery rate (FDR, 10%) analysis detected changes in 19 metabolites after 3 months and 7 metabolites after 1 year in participants, but changes in only 1 metabolite at 3 months in controls. At the 1-year examination, 87 differences in metabolite profiles distinguished participants from controls. Metabolites changing significantly in abundance were matched to primarily plant-derived compounds associated with inflammation and platelet aggregation in metabolomics databases (METLIN and Madison Metabolomics Consortium Database). Principal component analysis (PCA) showed clear differences in metabolite abundance during the program and distinct profiles of metabolite change in participants with diagnosed heart disease compared to those with only elevated risk factors (Figure 2 below).

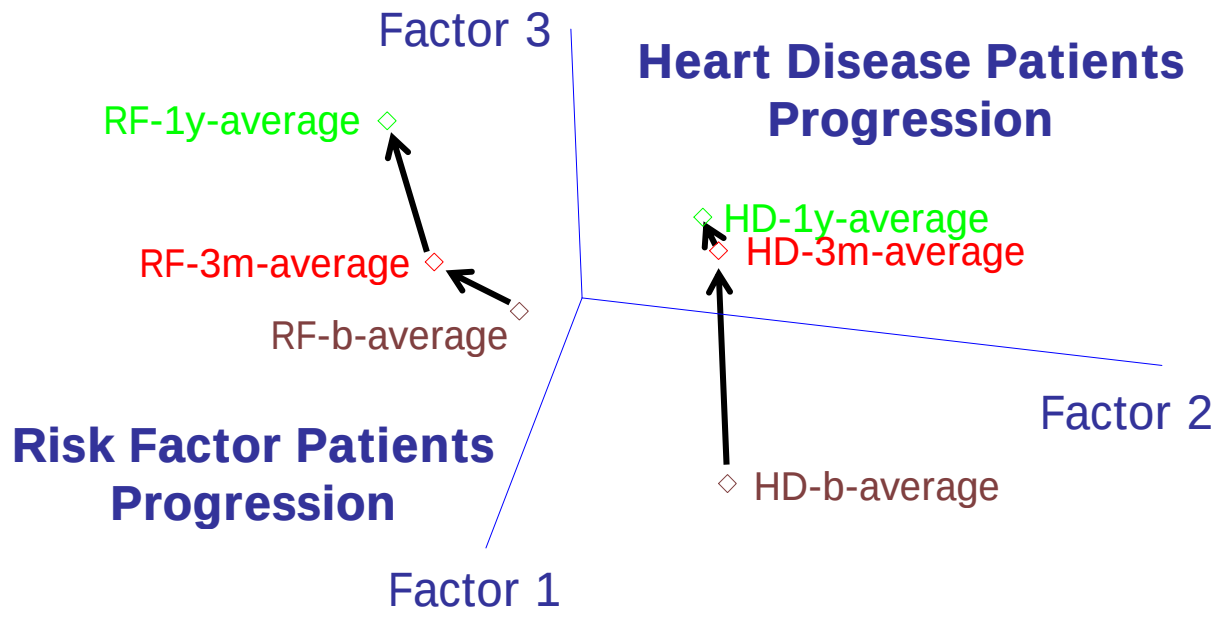



**Figure 2.** Principle Component Analysis of metabolomic data for participants in the Ornish program. Top panel: PCA grouping of participants stratified by overt heart disease (HD) or risk factors only (RF) at each time point; Bottom panel: Progression in metabolomic profiles over time in participants from the heart disease and risk factor groups.

Based on this preliminary analysis of the pilot data, an abstract was submitted to the American Heart Association for an upcoming meeting. Additional samples will be run during the coming year and new results will be combined with the previously analyzed data in updated analyses.

**Structural and Functional Measures of Cardiovascular Health**

Specific endpoints measured include ejection fraction and wall motion, coronary artery calcification scores, left and right ventricular volumes, myocardial mass, stenosis sizing and vessel diameter, plaque density and differentiation of calcified versus non-calcified plaque, and

tissue perfusion and viability. Work continues on the quantification and interpretation of the huge volumes of imaging data we have acquired. The research data will continue to be analyzed in the coming year; the data will help to provide a more comprehensive picture of the effects of the program on cardiac health.

**Proteomics**

During the year, we focused attention on analysis of the LC/MS/MS datasets collected from selected Ornish participants and control subjects. A total of 108 datasets derived from plasma collected at three time points of 36 subjects (cases) were processed using ProteoIQ tool (Bioinquire) to examine protein expression differences between three time points. Proteomic analysis by LC/MS/MS on 23 plasma samples was repeated for confirmation.

To derive protein expression data from the raw LC/MS/MS files generated in triplicate from 108 plasma samples, the datasets were first processed using Bioworks (3.3) and the processed data were searched against the IPI Human database (forward and reverse - concatenated). The SRF files (archived protein results) generated from Bioworks were grouped by ProteoIQ (1.5) to validate the protein identifications (using a 1% proFDR false discovery rate) and to derive protein expression differences between the time points.

The ProteoIQ tool has a built-in ProValT3 algorithm which provides automated false discovery rate (FDR) analysis by comparing results searched against a target and decoy database and assigns FDRs at the protein or peptide level. The integration of enhanced visualization tools in ProteoIQ enable data mining on the validated protein datasets for label-free quantitation between samples or groups using spectral counts, comparison of technical replicate runs for reproducibility, grouping of samples, and report generation. In order to quantify protein expression changes that occur between the time points, we used a spectral counting approach on the processed LC/MS/MS datasets (database search results). In spectral counting, the total number of MS/MS spectra that match peptides to a particular protein is used to measure the abundance of proteins in a complex mixture.

The finalized LC/MS/MS datasets were searched against an IPI human protein database containing both forward and reverse sequences using the Sequest search engine to generate protein lists for each sample. The database search generated protein results from plasma samples that were organized into three biological groups (time points) using ProteoIQ. Next, peptide identifications were parsed and clustered in order to estimate the FDR. Approximately 200 protein groups were identified at a 1% FDR with one or more tryptic peptides from all datasets. Relative protein expression (normalized spectral counts) across biological groupings for proteins identified in 75% of replicate analyses is shown in Figure 3 below.

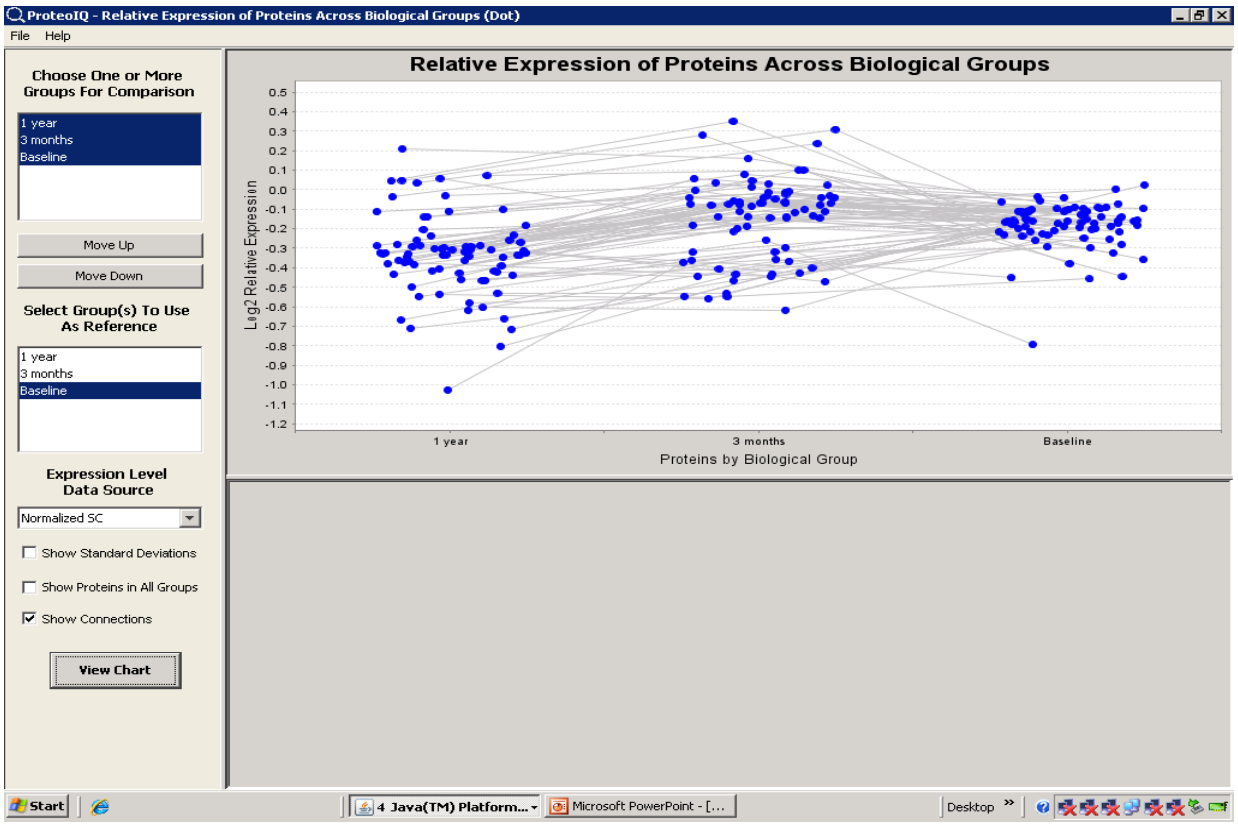



**Figure 3.** Relative protein expression differences between three time points.

Recent efforts focused on linking biological function to the lists of proteins derived from the ProteoIQ analysis of CVD datasets through the integration of fully annotated protein databases to the ProteoIQ module. Enhanced ProteoIQ tools offer the ability to create and add functional annotations to the protein databases and the annotation system of proteoIQ provides functionality for using available standard ontologies such as those available from the gene ontology (GO) project in addition to custom user-defined annotations. The ProteoIQ will summarize the protein annotations in charts to visualize the groups by functional characterization and protein expression. GO terms that were enriched between the CVD time points are shown in Figure 4. We are continuing to mine the proteomics datasets using ProteoIQ to identify significantly enriched GO terms associated with the time points to understand the biological processes that reduce the CVD risk factors in the Ornish participants.

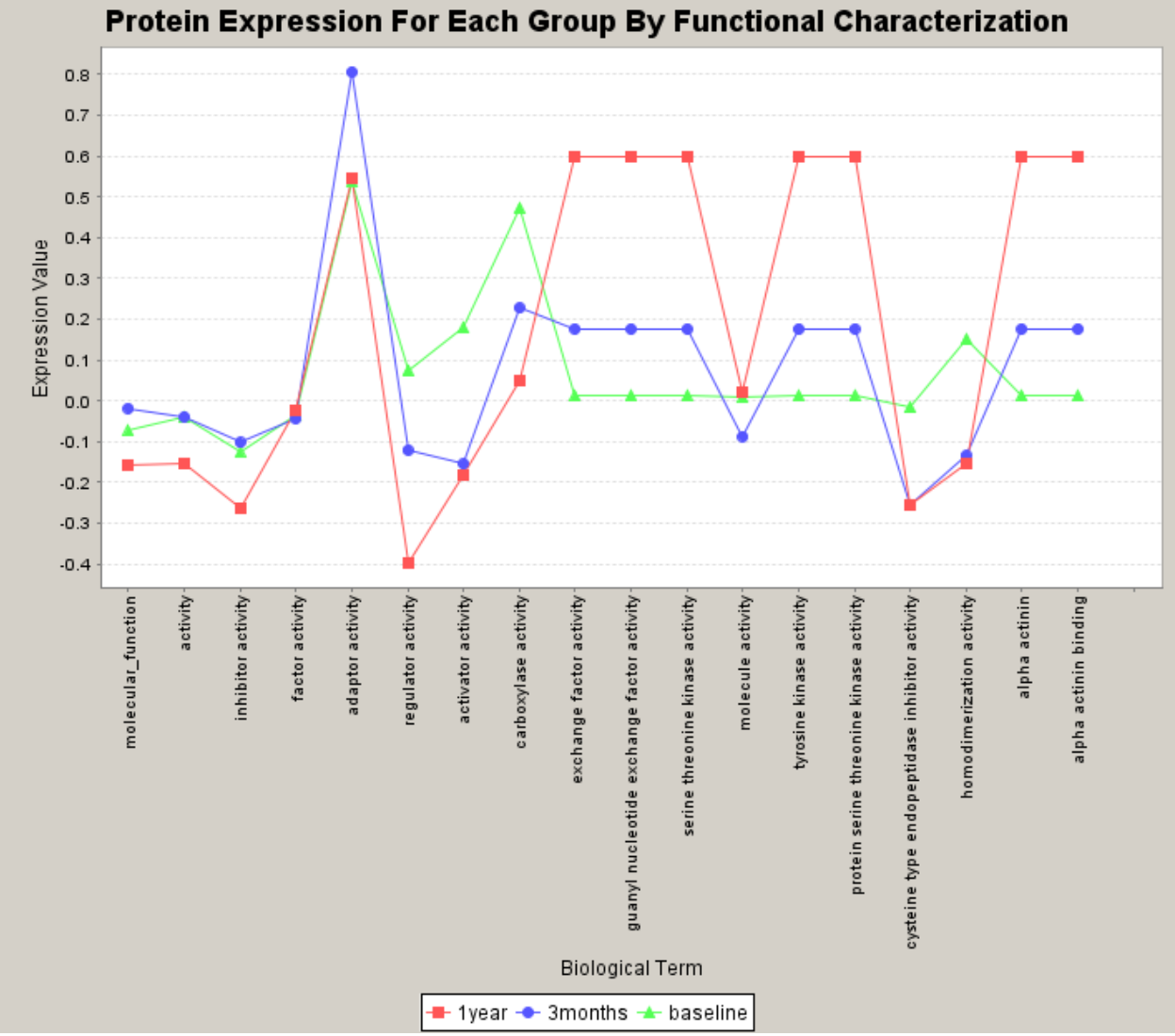



**Figure 4.** GO terms that were enriched between the CVD time points.

We have 24 matched case/control pairs completed for protein analysis. We have identified 8 additional participants who match previously run samples. These 8 samples will be run on the LTQ-FT to generate a total of 32 matched pairs for the final analysis.

**Global Profiling of Gene/Protein Expression and Single Nucleotide Polymorphisms Associated with Coronary Heart Disease Reversal, Sub-Study for Previous Subjects in the Dr. Dean Ornish Program for Reversing Heart Disease**.

The primary objective of this study is to examine associations between DNA variation (in the form of 500,000+ single nucleotide polymorphisms) and participant response to the program. We are examining the influence of innate genetic variation on overall response, quantified as the risk of future cardiac events (Framingham risk), as well as response of specific cardiovascular disease risk factors. The main hypothesis is that innate variation in genes associated with lipid metabolism, protein biosynthesis, protein modification, transcription regulation and/or cell surface receptors (or other genes) will correlate positively with response to intensive lifestyle changes involving diet, exercise, meditation, yoga and group support, which may lead to improved CHD risk factor profiles and genetic markers of coronary artery disease

reversal or stabilization. Participants in this study are being recruited from previous cohorts of the Dr. Dean Ornish Program for Reversing Heart Disease at Windber Medical Center (prior to implementation of the primary Molecular Profiling Protocol described above).

**Status:**

During the year, we profiled individual SNPs defined in recent genome-wide association studies to have an impact on CVD (or associated risk factors) development. All of the SNPs examined this year were selected from previously published genome-wide association studies and were related to specific traits such as BMI, blood pressure, and lipid levels in the general population. We are determining if SNPs that have been shown to influence CVD-related traits in the general population influence how these traits respond during participation in the Ornish program.

Our summer intern, Marisa Hicks, did an excellent job completing TaqMan® genotyping on 186 Ornish participants (117 Ornish samples and 69 Ornish Sub-Study samples) for 13 SNPs using the ABI 7000 platform (rs6548238, rs1378942, rs2568958, rs9939609, rs17782313, rs7498665, rs17367504, rs16998073, rs646776, rs780094, rs3846662, rs3905000, rs12272004). In total, Marisa generated 2418 genotypes. Genotyping data also was completed on three additional SNPs (rs1530440, rs11191548, rs12946454). The results were confirmed for rs1530440 and rs11191548 by performing restriction fragment length polymorphism (RFLP) analysis with the restriction enzymes *Nde* I and *Hpy*CH4IV, respectively. These analyses genotyped 558 samples by TaqMan® assays and 372 samples by RFLP.

The following SNPs were analyzed for the corresponding traits: rs11191548 — systolic blood pressure; rs12946454 — systolic blood pressure; rs1378942 — diastolic blood pressure; rs1530440 — diastolic blood pressure; rs16998073 — diastolic blood pressure; rs2568958 — BMI and body weight; rs3846662 — HDL, LDL, total cholesterol, and triglycerides; rs3905000 — HDL, LDL, total cholesterol, and triglycerides; rs6548238 — BMI and body weight; rs780094 — HDL, LDL, total cholesterol, and triglycerides; rs17367504 — systolic blood pressure; rs17782313 — BMI and body weight; rs7498665 — BMI and body weight; rs9939609 — BMI and body weight; rs646776 — HDL, LDL, total cholesterol, and triglycerides; rs12272004 — HDL, LDL, total cholesterol, and triglycerides.

An example of the TaqMan® genotyping output for rs3846662 is presented below (Figure 5).

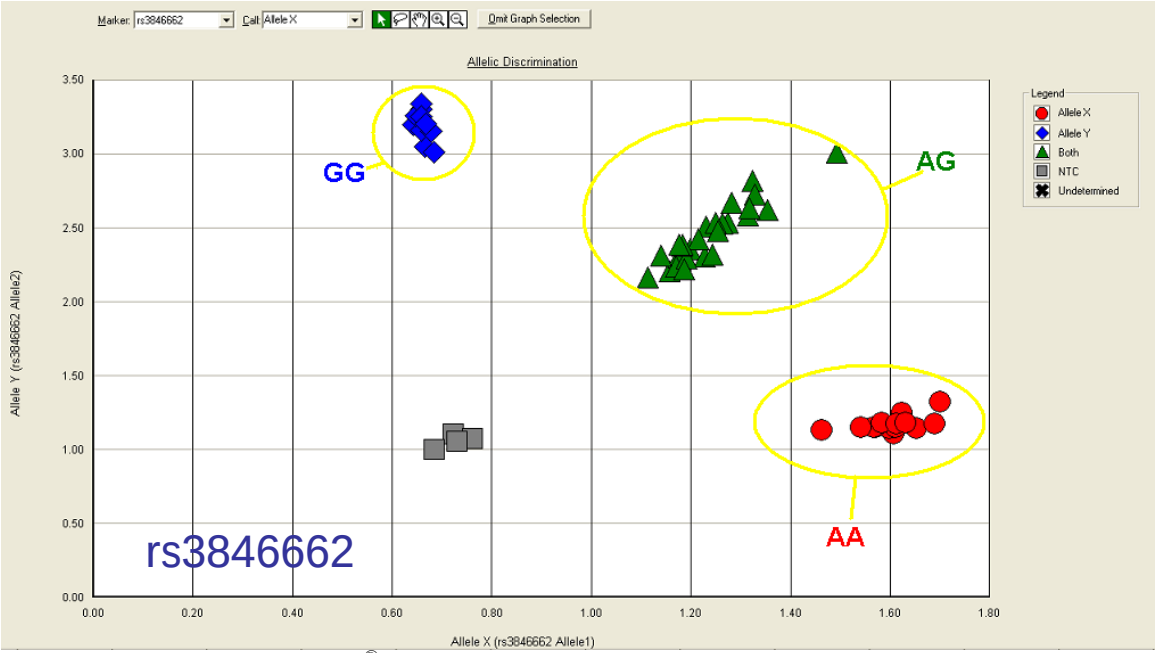



**Figure 5.** Example of TaqMan® genotyping output for rs3846662.

Results of the statistical analysis (Table 16 below) showed that genotype did not have an effect on change in BMI/weight, systolic or diastolic blood pressure, or HDL, LDL, or total cholesterol. However, response of triglycerides to the program was significantly influenced by several SNPs (Figure 6).

**Table 16. Response of selected CVD risk factors during participation in the Ornish program by genotype.**

| SNP | Variable | Genotype | n | Baseline[c] | p | Week 12[c] | % Change B to 12 w | Year 1[c] | % Change B to 1 y |
|---|---|---|---|---|---|---|---|---|---|
| rs11191548 | SBP | CC-CT | 31 | 133.5 ± 20.3 | 0.506 | 120.3 a ± 16.5 | -9.9% a | 127 ± 20.3 | -4.9% |
| | | TT | 145 | 135.9 ± 18.1 | | 123.4 b ± 14.8 | -9.2% b | 127.9 b ± 16.7 | -5.9% b |
| rs12946454 | SBP | AA | 93 | 136.2 ± 20.6 | 0.273 | 124.2 b ± 15.8 | -8.8% b | 127.5 b ± 16.5 | -6.4% b |
| | | AT | 74 | 133.6 ± 15.5 | | 121 b ± 13.6 | -9.4% b | 127.5 a ± 18.6 | -4.6% a |
| | | TT | 11 | 142.7 ± 15.1 | | 124.6 a ± 17.4 | -12.7% a | 130.9 ± 15.8 | -8.3% |
| | | AA | 93 | 136.2 ± 20.6 | 0.610 | 124.2 b ± 15.8 | -8.8% b | 127.5 b ± 16.5 | -6.4% b |
| | | AT-TT | 85 | 134.8 ± 15.7 | | 121.4 b ± 14.1 | -9.9% b | 128 a ± 18.2 | -5.0% a |
| rs1378942 | DBP | AA | 83 | 80.1 ± 9.8 | 0.243 | 72.7 b ± 8.7 | -9.2% b | 75.4 b ± 9.7 | -5.9% b |
| | | AC | 74 | 79.6 ± 10.9 | | 73.1 b ± 9.4 | -8.2% b | 75.5 a ± 9.6 | -5.2% a |
| | | CC | 21 | 83.8 ± 8.9 | | 73.7 b ± 8.6 | -12.1% b | 75.4 a ± 9.8 | -10.0% a |
| rs1530440 | DBP | CC | 116 | 80.8 ± 10.3 | 0.566 | 74 b ± 9.2 | -8.4% b | 75.7 b ± 10 | -6.3% b |
| | | CT | 49 | 79.5 ± 10.5 | | 71.4 b ± 8.7 | -10.2% b | 74.8 a ± 9.1 | -5.9% a |
| | | TT | 10 | 77.8 ± 9.1 | | 70.2 ± 7.3 | -9.8% | 74.8 ± 9.8 | -3.9% |
| | | CC | 116 | 80.8 ± 10.3 | 0.339 | 74 b ± 9.2 | -8.4% b | 75.7 b ± 10 | -6.3% b |
| | | CT-TT | 59 | 79.2 ± 10.2 | | 71.2 b ± 8.4 | -10.1% b | 74.8 a ± 9.1 | -5.6% a |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| rs16998073 | DBP | AA | 95 | 79.5 ± 9.4 | 0.296 | 71.8 b ± 9 | -9.7% b | 75.6 a ± 9.5 | -4.9% a |
| | | AT-TT | 82 | 81.1 ± 11 | | 74.3 b ± 8.8 | -8.4% b | 75.1 b ± 9.7 | -7.4% b |
| rs2568958 | BMI | AA | 83 | 32.62 ± 7.09 | 0.189 | 30.3 b ± 6.23 | -7.1% b | 29.4 b ± 6.25 | -9.9% b |
| | | AG | 75 | 33.04 ± 6.84 | | 30.73 b ± 6.52 | -7.0% b | 30.27 b ± 6.81 | -8.4% b |
| | | GG | 16 | 29.51 ± 7.36 | | 27.72 b ± 6.04 | -6.1% b | 27.16 a ± 5.59 | -8.0% a |
| | | AA | 83 | 32.62 ± 7.09 | 0.764 | 30.3 b ± 6.23 | -7.1% b | 29.4 b ± 6.25 | -9.9% b |
| | | AG-GG | 91 | 32.42 ± 7.03 | | 30.2 b ± 6.51 | -6.8% b | 29.73 b ± 6.69 | -8.3% b |
| | Wght | AA | 86 | 206.67 ± 47.13 | 0.120 | 191.84 b ± 41.55 | -7.2% b | 187.04 b ± 42.8 | -9.5% b |
| | | AG | 76 | 211.3 ± 44.98 | | 196.83 b ± 41.91 | -6.8% b | 193.34 b ± 43.7 | -8.5% b |
| | | GG | 16 | 185.16 ± 43.23 | | 173.03 b ± 35.51 | -6.6% b | 169.22 b ± 34.5 | -8.6% b |
| | | AA | 86 | 206.67 ± 47.13 | 0.991 | 191.84 b ± 41.55 | -7.2% b | 187.04 b ± 42.8 | -9.5% b |
| | | AG-GG | 92 | 206.75 ± 45.55 | | 192.7 b ± 41.68 | -6.8% b | 189.14 b ± 43.1 | -8.5% b |
| rs3846662 | HDL | AA | 39 | 47.3 ± 12.5 | 0.123 | 39.4 b ± 8.5 | -16.7% b | 45.6 ± 11.7 | -3.6% |
| | | AG | 102 | 47.7 ± 13 | | 41 b ± 9.5 | -14.0% b | 45.9 ± 10 | -3.8% |
| | | GG | 35 | 42.7 ± 11.9 | | 37 b ± 9 | -13.3% b | 40.9 ± 10.3 | -4.2% |
| | LDL | AA | 37 | 119.7 ± 41.9 | 0.148 | 95.8 b ± 32.4 | -20.0% b | 105 a ± 36.3 | -12.3% a |
| | | AG | 97 | 112.4 ± 35.1 | | 98.3 b ± 31.7 | -12.5% b | 108.1 ± 31 | -3.8% |
| | | GG | 35 | 104.3 ± 31.9 | | 87.7 a ± 26.1 | -15.9% a | 92.5 a ± 22 | -11.3% a |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | TC | AA | 39 | 202.6 ± 48 | 0.079 | 166 b ± 38.6 | -18.1% b | 185.4 a ± 42.3 | -8.5% |
| | | AG | 102 | 196.5 ± 42.6 | | 171.5 b ± 39.1 | -12.7% | 184 a ± 38.2 | -6.4% a |
| | | GG | 35 | 180.8 ± 38.6 | | 158.5 b ± 32.5 | -12.3% b | 163.3 a ± 30 | -9.7% a |
| | Trigs | AA | 39 | 170 ± 80.6 | 0.618 | 154.6 ± 78.8 | -9.1% | 174.5 ± 109.5 | 2.6% |
| | | AG | 102 | 183.3 ± 100.9 | | 162.8 a ± 75.6 | -11.2% a | 156.3 a ± 80.8 | -14.7% a |
| | | GG | 35 | 168.7 ± 79.9 | | 169.6 ± 75.2 | 0.5% | 158.5 ± 63.5 | -6.0% |
| | Trigs | AA | 39 | 170 ± 80.6 | 0.570 | 154.6 ± 78.8 | -9.1% | 174.5 ± 109.5 | 2.6% |
| | | AG-GG | 137 | 179.6 ± 95.9 | | 164.6 ± 75.3 | -8.4% | 156.8 a ± 76.6 | -12.7% a |
| | | AG-AA | 141 | 179.6 ± 95.7 | 0.534 | 160.6 a ± 76.3 | -10.6% a | 161.3 a ± 89.6 | -10.2% a |
| | | GG | 35 | 168.7 ± 79.9 | | 169.6 ± 75.2 | 0.5% | 158.5 ± 63.5 | -6.0% |
| rs3905000 | HDL | AA-AG | 45 | 45.4 ± 12.3 | 0.462 | 38.6 b ± 8.7 | -15.0% b | 43 ± 9.6 | -5.3% |
| | | GG | 133 | 47 ± 12.9 | | 40.2 b ± 9.5 | -14.5% b | 45.4 ± 10.7 | -3.4% |
| | LDL | AA-AG | 44 | 114.6 ± 36 | 0.761 | 100.9 a ± 31 | -12.0% a | 106.3 ± 34.4 | -7.2% |
| | | GG | 127 | 111.7 ± 36.2 | | 93.8 b ± 30.6 | -16.0% b | 104.2 a ± 30.4 | -6.7% a |
| | TC | AA-AG | 45 | 195.2 ± 42.3 | 0.953 | 173 b ± 35.7 | -11.4% b | 179.9 a ± 38 | -7.8% a |
| | | GG | 133 | 194.8 ± 43.8 | | 165.9 b ± 38.3 | -14.8% b | 181.1 b ± 39 | -7.0% b |
| | Trigs | AA-AG | 45 | 180.7 ± 99.6 | 0.807 | 168.8 ± 77.6 | -6.6% | 154.8 ± 68.9 | -14.3% |
| | | GG | 133 | 176.8 ± 89.9 | | 159.8 a ± 75.1 | -9.6% a | 163.2 ± 89.4 | -7.7% |

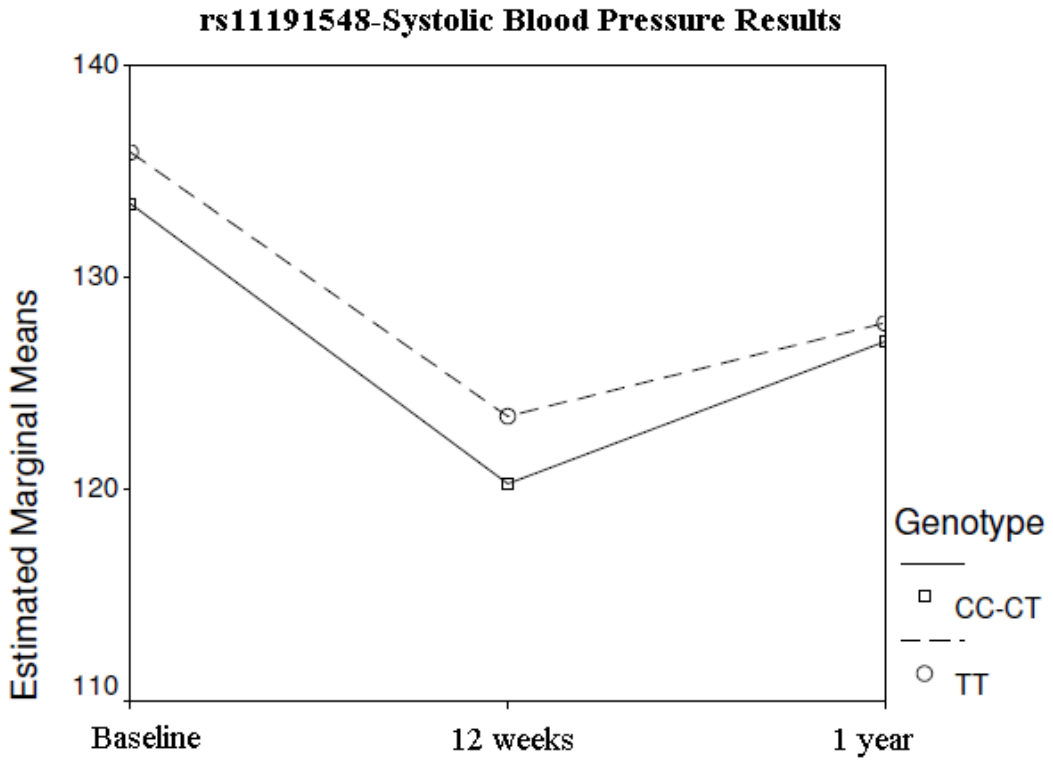
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| rs6548238 | BMI | CC | 114 | 32.29 ± 7 | 0.536 | 30.02 b ± 6.22 | -7.0% b | 29.35 b ± 6.5 | -9.1% b |
| | | CT-TT | 59 | 32.85 ± 7.21 | | 30.59 b ± 6.66 | -6.9% b | 29.93 b ± 6.4 | -8.9% b |
| | Wght | CC | 117 | 205.62 ± 45.19 | 0.678 | 190.86 b ± 40.0 | -7.2% b | 187.0 b ± 43.1 | -9.1% b |
| | | CT-TT | 60 | 208.68 ± 48.76 | | 194.89 b ± 44.9 | -6.6% b | 190.2 b ± 43.3 | -8.9% b |
| rs780094 | HDL | CC | 60 | 44.9 ± 10 | 0.070 | 38.2 b ± 7.6 | -14.9% b | 44.1 ± 10.1 | -1.8% |
| | | CT | 77 | 45.8 ± 12 | | 39.9 b ± 9.6 | -12.9% b | 43.8 ± 10.3 | -4.4% |
| | | TT | 41 | 50.5 ± 16.5 | | 41.8 b ± 10.6 | -17.2% b | 47.7 ± 11.5 | -5.5% |
| | LDL | CC | 60 | 106.9 ± 32.6 | 0.210 | 92 b ± 28.8 | -13.9% b | 103 ± 33.5 | -3.6% |
| | | CT | 71 | 116.8 ± 38.3 | | 99.8 b ± 32.2 | -14.6% b | 106.8 a ± 29.6 | -8.6% a |
| | | TT | 40 | 113.2 ± 36.8 | | 93.9 b ± 30.8 | -17.0% b | 103.6 ± 31.6 | -8.5% |
| | TC | CC | 60 | 185.6 ± 39.6 | 0.120 | 161.5 b ± 34.2 | -13.0% b | 174.7 a ± 39.5 | -5.9% a |
| | | CT | 77 | 198.7 ± 44 | | 173.1 b ± 38.9 | -12.9% b | 184.2 a ± 37.6 | -7.3% a |
| | | TT | 41 | 201.3 ± 45.9 | | 166.6 b ± 39.6 | -17.2% b | 183.3 a ± 39.3 | -8.9% a |
| | Trigs | CC | 60 | 170 ± 90.8 | 0.688 | 156.6 ± 73.6 | -7.9% | 143.5 a ± 71.2 | -15.6% a |
| | | CT | 70 | 179.6 ± 94.2 | | 170.9 ± 84.4 | -4.8% | 174.6 ± 97.1 | -2.8% |
| | | TT | 41 | 185.7 ± 91.7 | | 153.7 a ± 59.1 | -17.2% a | 161.5 ± 73.8 | -13.0% |
| | | CT-CC | 137 | 175.4 ± 92.6 | 0.534 | 164.6 ± 79.9 | -6.2% | 161 ± 87.8 | -8.2% |
| | | TT | 41 | 185.7 ± 91.7 | | 153.7 a ± 59.1 | -17.2% a | 161.5 ± 73.8 | -13.0% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | CC | 60 | 170 ± 90.8 | 0.425 | 156.6 ± 73.6 | -7.9% | 143.5 a ± 71.2 | -15.6% a |
| | | CT-TT | 118 | 181.7 ± 93 | | 164.9 a ± 76.7 | -9.2% a | 170 ± 89.6 | -6.4% |
| rs17367504 | SBP | AA | 140 | 135.1 ± 18.8 | 0.493 | 121.8 b ± 15.4 | -9.8% b | 127 b ± 17.1 | -6.0% b |
| | | AG-GG | 38 | 137.4 ± 17.1 | | 126.8 a ± 13.2 | -7.7% a | 130.5 ± 17.9 | -5.0% |
| rs7498665 | BMI | AA | 67 | 31.88 ± 6.66 | 0.504 | 29.84 b ± 6.34 | -6.4% b | 29 b ± 6.57 | -9.0% b |
| | | AG | 80 | 32.78 ± 7.05 | | 30.31 b ± 6.11 | -7.5% b | 29.64 b ± 6.08 | -9.6% b |
| | | GG | 25 | 33.63 ± 8.09 | | 31.4 b ± 7.34 | -6.6% b | 31.08 b ± 7.52 | -7.6% b |
| | Wght | AA | 68 | 200.1 ± 44.1 | 0.243 | 186.02 b ± 40.0 | -7.0% b | 181.33 b ± 42.6 | -9.4% b |
| | | AG | 82 | 212.9 ± 48.2 | | 198.1 b ± 42.8 | -7.0% b | 193.75 b ± 43.0 | -9.0% b |
| | | GG | 26 | 206.0 ± 45.0 | | 191.9 b ± 41.2 | -6.8% b | 189.32 b ± 43.6 | -8.1% b |
| rs17782313 | BMI | CC-CT | 88 | 32.8 ± 7.0 | 0.550 | 30.5 b ± 6.4 | -7.1% b | 29.8 b ± 6.5 | -9.4% b |
| | | TT | 85 | 32.2 ± 7.1 | | 30.0 b ± 6.3 | -6.8% b | 29.4 b ± 6.5 | -8.7% b |
| | Wght | CC-CT | 90 | 207.1 ± 45.9 | 0.896 | 192.6 b ± 41.6 | -7.0% b | 188.0 b ± 43.4 | -9.2% b |
| | | TT | 87 | 206.2 ± 47.0 | | 191.9 b ± 41.9 | -6.9% b | 188.16 b ± 42.9 | -8.7% b |
| rs9939609 | BMI | AA | 36 | 32.6 ± 7.9 | 0.294 | 30.4 b ± 7.5 | -7.0% b | 29.5 b ± 7.6 | -9.5% b |
| | | AT | 80 | 31.6 ± 6.16 | | 29.6 b ± 5.6 | -6.4% b | 29.1 b ± 5.6 | -7.8% b |
| | | TT | 57 | 33.7 ± 7.6 | | 31.1 b ± 6.6 | -7.7% b | 30.2 b ± 7.0 | -10.3% b |
| | Wght | AA | 36 | 210.7 ± 51.2 | 0.312 | 195.7 b ± 48.7 | -7.1% b | 190.0 b ± 51.1 | -9.8% b |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | AT | 83 | 201 ± 39.7 | | 188.5 b ± 36.2 | -6.2% b | 185.9 b ± 36.7 | -7.5% b |
| | | TT | 58 | 212.2 ± 51.6 | | 195.4 b ± 44.4 | -7.9% b | 190.1 b ± 46.5 | -10.4% b |
| rs12272004 | HDL | AC | 25 | 44.7 ± 8.5 | 0.452 | 39.0 b ± 6.5 | -12.8% b | 42.9 ± 8.7 | -4.0% |
| | | CC | 152 | 46.8 ± 13.3 | | 39.9 b ± 9.7 | -14.7% b | 45.1 a ± 10.9 | -3.6% a |
| | LDL | AC | 23 | 102.6 ± 23.5 | 0.268 | 91.2 ± 22.3 | -11.1% | 97.8 ± 26.9 | -4.7% |
| | | CC | 147 | 114 ± 37.6 | | 96.3 b ± 32 | -15.5% b | 105.5 a ± 31.8 | -7.5% a |
| | TC | AC | 25 | 184.4 ± 30.9 | 0.198 | 163.7 a ± 26.4 | -11.2% a | 174.6 ± 38 | -5.3% |
| | | CC | 152 | 196.5 ± 45 | | 168.3 b ± 39.4 | -14.4% b | 181.3 b ± 38.5 | -7.7% b |
| | Trigs | AC | 25 | 172.2 ± 88.3 | 0.744 | 170.8 ± 70.2 | -0.8% | 172.8 ± 122 | 0.3% |
| | | CC | 152 | 178.7 ± 93.4 | | 161 a ± 76.7 | -9.9% a | 158.7 a ± 77.2 | -11.2% a |
| rs646776 | HDL | CC-CT | 68 | 46.7 ± 10.9 | 0.901 | 39.3 b ± 7.6 | -15.8% b | 45.1 ± 10.3 | -3.4% |
| | | TT | 108 | 46.4 ± 13.9 | | 40.1 b ± 10.2 | -13.6% b | 44.6 ± 10.9 | -3.9% |
| | LDL | CC-CT | 63 | 108.3 ± 29.3 | 0.413 | 96.1 a ± 26.8 | -11.3% a | 103.8 ± 27.6 | -4.2% |
| | | TT | 106 | 114.9 ± 39.8 | | 95.4 b ± 33.2 | -17.0% b | 104.8 a ± 33.4 | -8.8% a |
| | TC | CC-CT | 68 | 193.2 ± 34.4 | 0.705 | 168.7 b ± 31.7 | -12.7% b | 182 a ± 33.2 | -5.8% a |
| | | TT | 108 | 195.7 ± 48.5 | | 166.9 b ± 41.5 | -14.7% b | 179.2 b ± 41.6 | -8.4% b |
| | Trigs | CC-CT | 68 | 185.1 ± 105.4 | 0.380 | 170.3 ± 85.3 | -8.0% | 169.8 ± 95.4 | -8.3% |
| | | TT | 108 | 172.5 ± 83.6 | | 156.8 ± 69.1 | -9.1% | 154.5 a ± 77.3 | -10.4% a |

[a] Different than Baseline value at $p < 0.05$ based on a repeated-measures ANOVA (3 time points as within-subjects factor with Cohort Type as the between-subjects factor) using a Bonferroni adjustment for multiple comparisons by time point / cohort type / gender within cohort.
[b] Different than Baseline value at $p < 0.001$ based on a repeated-measures ANOVA (3 time points as within-subjects factor with Cohort Type as the between-subjects factor) using a Bonferroni adjustment for multiple comparisons by time point / cohort type / gender within cohort.
[c] Based on descriptive statistics from the Baseline / Week 12 / Year 1 Repeated-Measures ANOVAs.


rs2568958-Body Weight Results
210
200
190
180
Estimated Marginal Means
Baseline
12 weeks
1 year
Genotype
AA
AG-GG


rs11191548-Systolic Blood Pressure Results
140
130
120
110
Estimated Marginal Means
Baseline
12 weeks
1 year
Genotype
CC-CT
TT

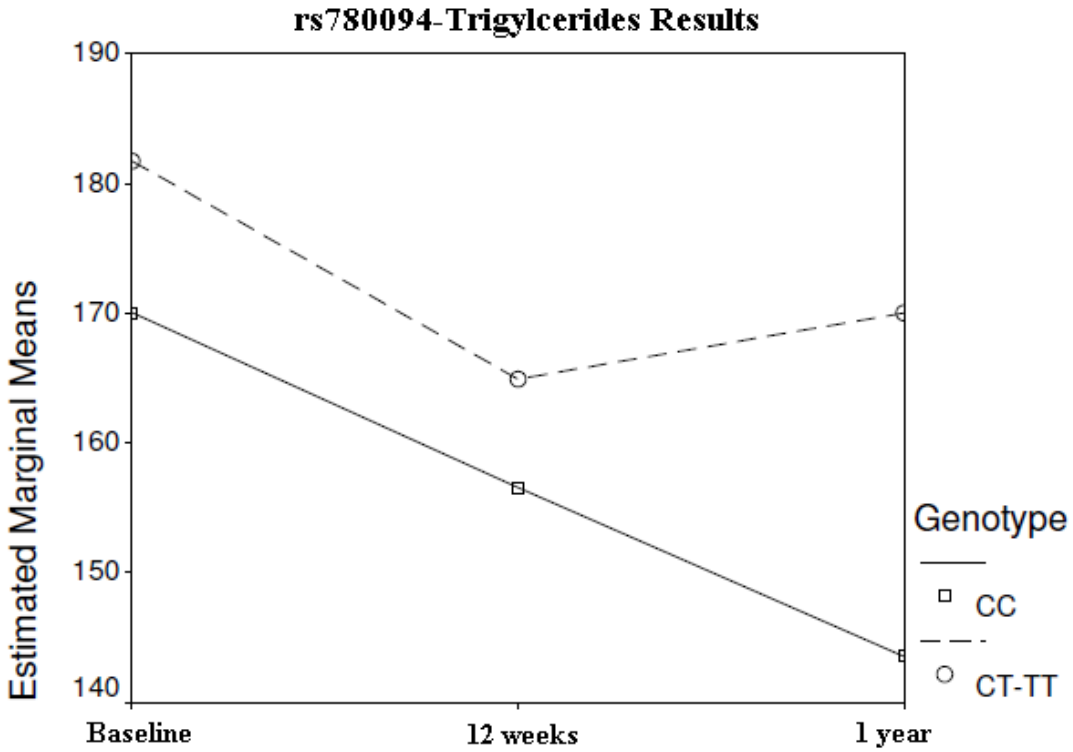



**Figure 6.** Change in selected CVD risk factors by SNP genotype.

Genotyping for the following 8 SNPs is currently in progress: rs964184, rs1260326, rs2954029, rs10401969, rs17321515, rs17145738, rs16996148, and rs4846914.

**Task #7: Enrollment to "Acute Endothelial Dependent Response to Distinct Macronutrient Challenges Study: A Comparison of Brachial Reactivity Reponses to a Low Carbohydrate/High Fat, High Carbohydrate/Low Fat, or an AHA Meal in Subjects at Risk for Coronary Heart Disease" protocol.**

**Status:** Task complete. Study design and methodology described in previous reports. The following manuscript has been published (see Appendix B) and describes study outcome measures:

Miller M, Beach V, Sorkin JD, et al. Comparative effects of three popular diets on lipids, endothelial function, and C-reactive protein during weight maintenance. *J Am Diet Assoc.* Apr 2009;109(4):713-717.

**Task #7 (replaced old Task #7 from FY07 SOW and renumbered to Task 11 in FY09 SOW): Expand the translational clinical and research program to a larger segment of the population by creating a Cardiovascular Risk Clinic (CRC).**

**Status**: Study is currently ongoing.

Background:
This program is being established as a platform to address the unique needs of retired military beneficiaries at risk for CV disease. The program mirrors the Cardiac Prevention Program (CPP) designed and established by the ICHP at WRAMC. It includes conventional and novel CV risk

profiling and tailored, personalized behavioral recommendations for primary or secondary prevention by an integrative team of providers comprised of a nurse case manager, psychologist, nurse practitioners, dietitians, stress management instructors, and exercise physiologists. Validated tools to screen for and measure CV risk, stress, sleep health, compliance with dietary recommendations and exercise are standard of care. The program is an adjunct to the best medical practices provided by their primary care provider.

Phase I of the program involves each participant undergoing a comprehensive health risk assessment that is completed by a physician, followed by a four- hour "Pearls for your Heart" workshop and participants then schedule individual appointments with each modality specialist to receive education and counseling in nutrition, exercise, stress management and mind/body health. These are monthly appointments to be completed over a 4-6 month period.

Phase II of the program begins after the completion of the healthy lifestyle intervention (Phase I). During this phase each participant will again meet with the physician. During this appointment the physician will prepare the participants for the next phase and give them strategies for maintaining success on their own. The second phase of the Program provides additional reinforcement through monthly phone calls with an integrative health coach. Participants will remain in Phase 2 for five years, during which time they will come to the center for re-assessments every six months.

Subject Enrollment and Demographics:
Total subject enrollment in the CRC is 60 participants; currently 54 participants remain active in the study. Of the total participants, 30 were randomized to the intervention arm of the study (currently 26 participants remain active) and 30 participants were randomized to the control arm (28 remain active). Demographic characteristics of participants are: average age 61.8 years, 32% female, 17% veterans or the spouse of a veteran, and 22% with diagnosed coronary heart disease.

Blood was collected and processed for 107 participant-time points for the CRC program. Approximately 2,157 sample aliquots were made as summarized below:

| | | | |
|---|---|---|---|
| Participant-time points | 107 | | |
| PAXGene Tubes | 116 | | |
| RBCs | 240 | | |
| Plasma samples | | Serum samples | |
| NMR lipids | 121 | Adiponectin | 116 |
| Leptin | 121 | Serum amyloid A | 116 |
| CRP | 121 | Vitamin D | 116 |
| Resistin | 121 | Lp(a) | 116 |
| Insulin | 121 | Extra Serum | 447 |
| Extra plasma | 339 | | |

Outcome Data
The intervention cohorts have shown change in the desired direction for virtually all of the measured coronary artery disease (CAD) risk factors over the initial 4-6 month period (Table 17A). Measures of obesity including weight and BMI declined ~3.5%. Levels of total cholesterol were reduced by ~8% and triglycerides dropped by 21%. Systolic blood pressure decreased by nearly 8% and diastolic blood pressure by ~6%. HgbA1c, a marker of blood sugar levels over a three month period, decreased by 5%. Measures of carotid intimal-medial thickness (IMT) also were significantly lower after the intervention phase. This data demonstrates that lifestyle change programs may be important for primary prevention in individuals with diagnosed CAD and those at increased risk of disease. Results from the first longer-term follow up time point are shown in Table

17B. Over the course of approximately 8-10 months, diastolic blood pressure, maximum IMT, and glycosylated hemoglobin decreased significantly.

**Table 17A. Comparison of "Baseline" to "Intervention Complete" (4-6 months) data for 19 participants in the intervention arm of the Cardiovascular Risk Clinic**

| Category / Metrics | N | Average Baseline Value (SD) | Average Intervention Complete Value (SD) | Average Change | P-Value |
|---|---|---|---|---|---|
| Weight (lbs.) | 19 | 198.19 (47.8) | 191.21 (41.4) | -7.0 | <0.01 |
| Body Mass Index | 19 | 30.27 (4.4) | 29.12 (3.7) | -1.2 | <0.01 |
| Total Cholesterol (mg/dl) | 17 | 188.65 (48.0) | 174.00 (41.8) | -14.6 | <0.05 |
| High Density Lipids (mg/dl) | 17 | 53.35 (9.4) | 49.53 (8.1) | -3.8 | <0.05 |
| Low Density Lipids (mg/dl) | 17 | 112.29 (38.2) | 104.59 (34.3) | -7.7 | 0.2849 |
| Triglycerides (mg/dl) | 17 | 126.47 (62.2) | 99.71 (37.5) | -26.8 | <0.05 |
| Systolic Blood Pressure | 18 | 134.22 (22.0) | 124.11 (17.1) | -10.1 | <0.01 |
| Diastolic Blood Pressure | 18 | 79.33 (10.9) | 74.33 (7.0) | -5.0 | <0.05 |
| Depression Scale [CES-D] | 18 | 10.39 (10.1) | 7.11 (5.8) | -3.3 | 0.0588 |
| Hostility Scale [Cook-Medley] | 18 | 6.83 (4.3) | 5.78 (3.4) | -1.1 | 0.0864 |
| Perceived Stress Scale [PSS] | 18 | 12.06 (7.2) | 11.56 (5.5) | -0.5 | 0.7525 |
| Daily Total Fat (grams) | 0 | --- | --- | --- | --- |
| Daily Saturated Fat (grams) | 0 | --- | --- | --- | --- |
| Avg. CCA/Mean IMT | 18 | 0.870 (0.1331) | 0.811 (0.1114) | -0.059 | <0.05 |
| Avg. CCA / Max IMT | 18 | 0.996 (0.1344) | 0.918 (0.1124) | -0.1 | <0.01 |
| Fasting Glucose (mg/dl) | 18 | 98 (13.3) | 104 (26.5) | 5.8 | 0.2984 |
| HgbA1c | 17 | 6.0 (1.15) | 5.8 (1.02) | -0.3 | <0.001 |
| Cortisol | 17 | 12.9 (4.37) | 14.7 (4.08) | 1.8 | 0.1652 |
| TSH | 17 | 1.95 (1.168) | 1.92 (1.260) | 0.0 | 0.7717 |
| Epworth Sleepiness Scale (0 to 24) | 18 | 7 (4.3) | 7 (4.0) | 0.0 | 1.0000 |
| Pittsburgh Sleep Quality Index (0-21) | 17 | 8 (4.7) | 6 (3.3) | -1.7 | <0.05 |

**Table 17B. Change in outcome variables after 8-10 months for 8 participants in the intervention arm of the Cardiovascular Risk Clinic**

| Category / Metrics | N | Average Baseline Value (SD) | Average 8-10 month value (SD) | Average Change | P-Value |
|---|---|---|---|---|---|
| Weight (lbs.) | 8 | 189.32 (49.9) | 179.55 (40.4) | -9.8 | 0.0614 |
| Body Mass Index | 8 | 29.19 (4.5) | 27.78 (2.7) | -1.4 | 0.0887 |
| Total Cholesterol (mg/dl) | 8 | 203.25 (43.6) | 193.63 (43.0) | -9.6 | 0.5899 |
| High Density Lipids (mg/dl) | 8 | 54.75 (11.3) | 56.50 (7.8) | 1.8 | 0.5439 |
| Low Density Lipids (mg/dl) | 8 | 125.50 (31.2) | 115.75 (36.4) | -9.8 | 0.5404 |
| Triglycerides (mg/dl) | 8 | 125.75 (64.2) | 105.88 (44.0) | -19.9 | 0.2507 |
| Systolic Blood Pressure | 8 | 125.75 (12.6) | 123.50 (17.1) | -2.3 | 0.6222 |
| Diastolic Blood Pressure | 8 | 76.25 (13.0) | 66.75 (7.1) | -9.5 | <0.05 |
| Depression Scale [CES-D] | 5 | 9.20 (10.1) | 10.00 (14.0) | 0.8 | 0.9166 |
| Hostility Scale [Cook-Medley] | 5 | 6.60 (5.2) | 5.40 (3.0) | -1.2 | 0.5473 |
| Perceived Stress Scale [PSS] | 5 | 11.80 (8.4) | 12.80 (12.0) | 1.0 | 0.8383 |
| Avg. CCA/Mean IMT | 6 | 0.864 (0.1561) | 0.826 (0.1669) | -0.038 | 0.0923 |
| Avg. CCA / Max IMT | 6 | 0.995 (0.1480) | 0.912 (0.1723) | -0.1 | <0.05 |
| Fasting Glucose (mg/dl) | 8 | 95 (8.0) | 93 (8.6) | -1.1 | 0.3375 |

| | | | | | |
|---|---|---|---|---|---|
| **HgbA1c** | 8 | 5.7 (0.26) | 5.5 (0.27) | -0.3 | <0.01 |
| **Cortisol** | 8 | 12.4 (5.84) | 13.7 (2.38) | 1.2 | 0.5483 |
| **TSH** | 8 | 1.97 (1.008) | 1.96 (1.377) | 0.0 | 0.9738 |
| **Epworth Sleepiness Scale (0 to 24)** | 5 | 8 (6.1) | 6 (4.7) | -2.0 | 0.1662 |
| **Pittsburgh Sleep Quality Index (0-21)** | 5 | 10 (6.7) | 8 (5.4) | -1.4 | 0.5254 |

In subjects randomized to the control arm of the study, who do not participate in the lifestyle change intervention, many risk factors did not show significant changes after 6 months in the study (Table 18). HDL-cholesterol decreased by ~10%, cortisol increased by ~18%, and carotid IMT measures decreased significantly, but this may be a statistical anomaly attributable to the small sample size, wide inter-individual variability, and previous participation in another lifestyle change program by some of the control participants who could be continuing to practice previously learned healthy lifestyle changes. No control participants have yet reached the year 1 follow-up time point.

**Table 18. Change in outcome variables after 6 months for 19 participants in the control arm of the Cardiovascular Risk Clinic**

| Category / Metrics | N | Average Baseline Value (SD) | Average Waiting Period Complete Value (SD) | Average Change | P-Value |
|---|---|---|---|---|---|
| **Weight (lbs.)** | 17 | 199.14 (43.8) | 196.00 (41.8) | -3.1 | 0.0931 |
| **Body Mass Index** | 15 | 31.69 (6.5) | 31.30 (6.2) | -0.4 | 0.4239 |
| **Total Cholesterol (mg/dl)** | 19 | 204.05 (37.6) | 190.32 (38.8) | -13.7 | 0.0716 |
| **High Density Lipids (mg/dl)** | 19 | 57.58 (19.1) | 51.84 (13.8) | -5.7 | <0.01 |
| **Low Density Lipids (mg/dl)** | 19 | 121.11 (31.4) | 110.21 (31.5) | -10.9 | 0.1360 |
| **Triglycerides (mg/dl)** | 19 | 136.68 (71.1) | 141.26 (77.6) | 4.6 | 0.7532 |
| **Systolic Blood Pressure** | 19 | 135.79 (15.9) | 134.53 (22.6) | -1.3 | 0.8112 |
| **Diastolic Blood Pressure** | 19 | 82.84 (8.7) | 78.84 (11.0) | -4.0 | 0.0649 |
| **Depression Scale [CES-D]** | 18 | 10.22 (10.0) | 8.22 (10.0) | -2.0 | 0.1014 |
| **Hostility Scale [Cook-Medley]** | 18 | 7.50 (5.8) | 7.33 (6.3) | -0.2 | 0.7290 |
| **Perceived Stress Scale [PSS]** | 18 | 11.89 (8.1) | 11.33 (9.1) | -0.6 | 0.6238 |
| **Daily Total Fat (grams)** | 0 | --- | --- | --- | --- |
| **Daily Saturated Fat (grams)** | 0 | --- | --- | --- | --- |
| **Avg. CCA / Mean IMT** | 19 | 0.941 (0.1607) | 0.888 (0.1285) | -0.054 | <0.01 |
| **Avg. CCA / Max IMT** | 19 | 1.074 (0.1776) | 0.986 (0.1465) | -0.1 | <0.001 |
| **Fasting Glucose (mg/dl)** | 19 | 116 (45.4) | 113 (39.0) | -2.4 | 0.7187 |
| **HgbA1c** | 18 | 6.5 (1.40) | 6.3 (1.03) | -0.2 | 0.2865 |
| **Cortisol** | 19 | 12.4 (4.63) | 14.6 (4.31) | 2.2 | <0.05 |
| **TSH** | 18 | 1.72 (0.772) | 1.73 (0.859) | 0.0 | 0.9574 |
| **Epworth Sleepiness Scale (0 to 24)** | 18 | 9 (5.0) | 8 (4.4) | -1.1 | 0.3634 |
| **Pittsburgh Sleep Quality Index (0-21)** | 18 | 7 (4.5) | 7 (4.0) | -0.5 | 0.5877 |

Adverse Events: All adverse events are submitted to and adjudicated by the Windber Medical Center Institutional Review Board and TATRC after review by both the Principal Investigator and Medical Monitor. There have been 5 adverse events in the intervention arm of the study, all deemed serious events, and 7 adverse events in the control arm of the study, all serious events. A serious event is defined as occurring at any dose or intervention level that results in any of the following outcomes: (1) results in death, (2) a threat to life, (3) inpatient hospitalization or

prolongation of existing hospitalization, (4) persistent or significant disability or incapacity, (5) causes cancer, (6) is an overdose, or (7) any medical event that requires treatment to prevent one of the medical outcomes listed above. Therefore, all 12 events were considered serious due to inpatient hospitalizations. There were 4 non-cardiac and 1 cardiac adverse events in the intervention arm of the study. No deaths occurred and none of these adverse events were deemed to be study related. There were 4 non-cardiac and 3 cardiac adverse events in the control arm of the study. No deaths occurred and none of these adverse events were deemed to be study related.

NMR Lipid Panel

Participants continued to experience clinically-important improvements in a number of components of the NMR lipid panel, which gives detailed information on particle size and number for VLDL, HDL, and LDL (Table 19A) . These data are important because several studies have linked selected variables, such as LDL particle number (LDLP) more strongly to CAD risk than LDL-cholesterol. Recommended LDLP goals are <1000 nmol/L (<20th percentile) for high risk patients and <1300 nmol/L (<50th percentile) for moderately high-risk patients.

**Table 19A. Comparison of lipoprotein profiles from "Baseline" to "Intervention Complete" (4-6 months) in 18 participants enrolled in the intervention arm of the Cardiovascular Risk Clinic**

| Category / Metrics | Sample Size N | Average Baseline Value (SD) | Average Intervention Complete Value (SD) | Average Change | P Value Category |
|---|---|---|---|---|---|
| **VLDL Particle Concentrations (nmol/L)** | | | | | |
| **VLDL & Chylomicron Particles [VLDLCP]** | 18 | 67.89 (42.9) | 50.05 (29.8) | -17.8 | <0.05 |
| **Large VLDL & Chylomicrons Particles [VLCP]** | 18 | 2.67 (4.0) | 1.31 (1.7) | -1.4 | <0.05 |
| **Medium VLCPDL Particles [VMP]** | 18 | 27.18 (19.8) | 18.48 (17.4) | -8.7 | <0.01 |
| **Small VLCPDL Particles [VSP]** | 18 | 38.04 (24.1) | 30.25 (16.2) | -7.8 | 0.1005 |
| **LDL Particle Concentrations (nmol/L)** | | | | | |
| **Total LDL Particles [LDLP]** | 18 | 1315.00 (323.5) | 1226.67 (396.7) | -88.3 | 0.2864 |
| **IDL Particles [IDLP]** | 18 | 34.83 (45.0) | 45.11 (74.7) | 10.3 | 0.6296 |
| **Large LDL Particles [LLP]** | 18 | 412.83 (207.1) | 401.22 (277.9) | -11.6 | 0.6966 |
| **Small LDL Particles (total) [LSP]** | 18 | 867.28 (323.6) | 780.22 (459.5) | -87.1 | 0.3240 |
| **Medium Small LDL Particles [LMSP]** | 18 | 177.56 (66.5) | 162.00 (93.8) | -15.6 | 0.4319 |
| **Very Small LDL Particles [LVSP]** | 18 | 689.83 (260.4) | 618.17 (367.2) | -71.7 | 0.2994 |
| **HDL Particle Concentrations (µmol/L)** | | | | | |
| **HDL Particles (total) [HDLP]** | 18 | 37.27 (5.5) | 34.14 (4.6) | -3.1 | <0.01 |
| **Large HDL Particles [HLP]** | 18 | 8.18 (3.1) | 7.26 (2.9) | -0.9 | 0.0569 |
| **Medium HDL Particles [HMP]** | 18 | 3.98 (6.4) | 3.09 (4.2) | -0.9 | 0.3563 |
| **Small HDL Particles [HSP]** | 18 | 25.11 (7.3) | 23.79 (5.6) | -1.3 | 0.1438 |
| **Mean Particle Sizes (nm diameter)** | | | | | |
| **VLDL Size [VZ]** | 18 | 47.35 (5.1) | 49.40 (6.8) | 2.0 | 0.1296 |
| **LDL Size [LZ]** | 18 | 20.83 (0.6) | 20.87 (0.9) | 0.0 | 0.7456 |
| **HDL Size [HZ]** | 18 | 8.82 (0.3) | 8.85 (0.3) | 0.0 | 0.5513 |
| **Calculated Lipids (mg/dL)** | | | | | |
| **Triglyceride (total) [NTG]** | 18 | 117.28 (66.6) | 90.56 (44.9) | -26.7 | <0.05 |

| | | | | | |
|---|---|---|---|---|---|
| **VLDL & Chylomicron Triglyceride (total) [NVCTG]** | 18 | 80.28 (61.6) | 54.44 (37.3) | -25.8 | <0.01 |
| **HDL Cholesterol (total) [NHC]** | 18 | 54.11 (11.2) | 49.67 (8.9) | -4.4 | <0.05 |
| | | | | | |

In contrast, Table 19B outlines the NMR results for the participants enrolled in the control arm of the study and who did not participate in the intervention. Because these individuals were not participating in any intervention to alter lipid levels, we would expect no significant changes in NMR lipids. This comparison, does demonstrate the impact of the healthy lifestyle intervention in altering important measures of CAD risk.

**Table 19B. Comparison of lipoprotein profiles from "Baseline" to the "Waiting Period Complete" (6 month time point) in 18 participants enrolled in the control arm of the Cardiovascular Risk Clinic**

| Category / Metrics | Sample Size N | Average Baseline Value (SD) | Average 6 month Value (SD) | Average Change | P |
|---|---|---|---|---|---|
| **VLDL Particle Concentrations (nmol/L)** | | | | | |
| **VLDL & Chylomicron Particles [VLDLCP]** | 19 | 67.14 (35.2) | 74.02 (41.9) | 6.9 | 0.3614 |
| **Large VLDL & Chylomicrons Particles [VLCP]** | 19 | 3.25 (4.7) | 3.68 (4.9) | 0.4 | 0.6279 |
| **Medium VLCPDL Particles [VMP]** | 19 | 34.66 (22.3) | 36.51 (26.8) | 1.8 | 0.7539 |
| **Small VLCPDL Particles [VSP]** | 19 | 29.23 (16.2) | 33.83 (17.6) | 4.6 | 0.1831 |
| **LDL Particle Concentrations (nmol/L)** | | | | | |
| **Total LDL Particles [LDLP]** | 19 | 1466.58 (505.6) | 1278.74 (452.8) | -187.8 | <0.05 |
| **IDL Particles [IDLP]** | 19 | 49.26 (52.1) | 48.37 (42.4) | -0.9 | 0.9331 |
| **Large LDL Particles [LLP]** | 19 | 410.11 (259.0) | 384.68 (235.4) | -25.4 | 0.2065 |
| **Small LDL Particles (total) [LSP]** | 19 | 1007.00 (642.8) | 845.79 (544.6) | -161.2 | 0.0553 |
| **Medium Small LDL Particles [LMSP]** | 19 | 206.74 (136.5) | 177.21 (107.6) | -29.5 | 0.0966 |
| **Very Small LDL Particles [LVSP]** | 19 | 800.26 (508.2) | 668.63 (438.2) | -131.6 | 0.0519 |
| **HDL Particle Concentrations (µmol/L)** | | | | | |
| **HDL Particles (total) [HDLP]** | 19 | 36.77 (4.8) | 35.64 (5.2) | -1.1 | 0.1284 |
| **Large HDL Particles [HLP]** | 19 | 8.60 (5.5) | 7.94 (4.0) | -0.7 | 0.1335 |
| **Medium HDL Particles [HMP]** | 19 | 3.77 (4.2) | 4.07 (3.3) | 0.3 | 0.6898 |
| **Small HDL Particles [HSP]** | 19 | 24.40 (5.5) | 23.63 (5.8) | -0.8 | 0.2579 |
| **Mean Particle Sizes (nm diameter)** | | | | | |
| **VLDL Size [VZ]** | 19 | 49.28 (5.9) | 51.95 (7.6) | 2.7 | 0.0750 |
| **LDL Size [LZ]** | 19 | 20.85 (1.0) | 20.88 (1.0) | 0.0 | 0.6302 |
| **HDL Size [HZ]** | 19 | 8.91 (0.6) | 8.97 (0.5) | 0.1 | 0.1814 |
| **Calculated Lipids (mg/dL)** | | | | | |
| **Triglyceride (total) [NTG]** | 19 | 133.68 (70.9) | 141.53 (82.1) | 7.8 | 0.6114 |
| **VLDL & Chylomicron Triglyceride (total)** | 19 | 92.58 (66.5) | 103.89 (79.2) | 11.3 | 0.4500 |
| **HDL Cholesterol (total) [NHC]** | 19 | 57.05 (19.2) | 54.79 (13.7) | -2.3 | 0.2009 |

Biomarkers

Assays are being conducted for a panel of eight biomarkers, potentially important in CAD development: C-reactive protein, Leptin, Insulin, Adiponectin, Lipoprotein a, Serum Amyloid a, Vitamin D and Resistin are shown in Tables 20A-20B.

**Table 20A. Comparison of biomarkers in 17 participants enrolled in the intervention arm of the CRC after completion of the "Healthy Intervention" (4-6 month time point)**

| Category / Metrics | Sample Size N | Average Baseline Value (SD) | Average Intervention Complete Value (SD) | Average Change | P Value Category |
|---|---|---|---|---|---|
| | | | | | |
| **CRP [ug/ml** | 17 | 1.97 (2.3) | 2.35 (4.0) | 0.386 | 0.7555 |
| **Leptin [ng/ml]** | 17 | 20.52 (14.1) | 20.15 (16.1) | -0.368 | 0.9384 |
| **Insulin [uU/ml]** | 17 | 16.98 (13.5) | 18.12 (11.3) | 1.139 | 0.5717 |
| **Adiponectin [ug/ml]** | 16 | 13.33 (6.1) | 12.68 (5.4) | -0.642 | 0.7603 |
| **Lipoprotein A [mg/DL]** | 17 | 82.69 (91.2) | 66.09 (71.2) | -15.330 | 0.6545 |
| **Serum Amyloid A (MSD)** | 17 | 26.86 (6.1) | 28.65 (6.3) | 1.567 | 0.4502 |
| **Vitamin D [ng/ml]** | 0 | --- | --- | --- | --- |
| **Resistin [ng/ml]** | 17 | 12.36 (3.4) | 10.70 (2.9) | -1.665 | 0.1427 |

In contrast, Table 20B outlines the biomarker results for the participants enrolled in the control arm of the study and who did not participate in the intervention. We do not expect to see significant changes in CAD risk factors for control participants.

**Table 20B. Comparison of biomarkers in 19 participants enrolled in the control arm of the CRC after completion of the "Waiting Period" (6 month time point)**

| Category / Metrics | Sample Size N | Average Baseline Value (SD) | Average 6 month Value (SD | Average Change | P Value Category |
|---|---|---|---|---|---|
| **CRP [ug/ml** | 19 | 2.48 (3.2) | 2.65 (1.9) | 0.164 | 0.8841 |
| **Leptin [ng/ml]** | 19 | 16.13 (11.7) | 15.76 (11.6) | -0.365 | 0.9384 |
| **Insulin [uU/ml]** | 19 | 22.80 (22.5) | 17.43 (9.9) | -5.373 | 0.3743 |
| **Adiponectin [ug/ml]** | 19 | 11.65 (6.4) | 12.42 (11.1) | 1.859 | 0.6636 |
| **Lipoprotein A [mg/DL]** | 19 | 72.97 (102.1) | 75.35 (74.6) | 4.828 | 0.8905 |
| **Serum Amyloid A (MSD)** | 19 | 27.76 (8.0) | 29.56 (5.6) | 2.193 | 0.2787 |
| **Vitamin D [ng/ml]** | 0 | --- | --- | --- | --- |
| **Resistin [ng/ml]** | 19 | 11.75 (4.6) | 11.88 (4.7) | 0.135 | 0.9280 |

**Task #7a: Initiate Stress Therapy Empowering Prevention (STEP) component to the Cardiovascular Risk Assessment program outlined in Task #7 above (renumbered to Task 11 in FY09 SOW).**

**Status**: Study is currently ongoing.

Background:
This is a collaborative study involving researchers from Windber Research Institute and Walter Reed Army Medical Center and is modeled after the Caretakers Optimizing Readiness through Preventive Strategies (CORPS), designed by the Integrative Cardiac Health Program (ICHP) at Walter Reed Army Medical Center (WRAMC), except that it targets participants with chronic disease. The purpose of this task is to determine the degree of stress, sleep disturbance, and cardiovascular disease risk in patients who have been diagnosed with breast cancer or are at high risk of developing breast disease.

In the first part of the intervention, patients will be randomized to a 12 week Healthy Lifestyle intervention group or a non-intervention group. During this phase, each intervention participant undergo a comprehensive health risk assessment that is completed by a physician, followed by mandatory attendance to on-site group sessions in which they will participate in 1 hour of stress management, 30 minutes of nutrition education every week, and 30 minutes of exercise alternated with 30 minutes of mind/body health every other week. In addition, the nurse will provide educational lectures on various health topics during 4 sessions. After completing Phase I, patients will participate in a five year healthy lifestyle intervention or control group.

During phase II each intervention participant will again meet with the physician. During this appointment the physician will prepare the participants for the next phase and give them strategies for maintaining success on their own. The second phase of the program provides additional reinforcement through monthly phone calls with an integrative health coach. Participants will remain in Phase II for five years, during which time they will come to the center for re-assessments every six months.

We hypothesize that the 12 week healthy lifestyle interventions will significantly reduce stress, sleep disturbances, and cardiovascular risk in patients at risk for, or already diagnosed with, breast cancer.

Subject Enrollment and Demographics:
Total subject enrollment is 18; currently 16 participants remain active in the study. All 18 of these participants are enrolled in the intervention arm of the study. Demographic characteristics of participants are: average age 64.9 years, 28% veterans or the spouse of a veteran, 6% have diagnosed coronary heart disease, and 61% have breast cancer.

Twelve-week data collection and testing were completed on 33 participants. Approximately 687 aliquots were made as summarized by the following:

| | |
|---|---|
| Individual Participants | 33 |
| PAXGene Tubes | 36 |
| RBCs | 76 |

| Plasma samples | | Serum samples | |
|---|---|---|---|
| NMR lipids | 37 | Adiponectin | 37 |
| Leptin | 37 | Estradiol | 37 |
| Resistin | 37 | HER2 | 37 |
| TNFα | 37 | Serum amyloid A | 37 |
| Insulin | 37 | Vitamin D | 37 |
| CRP | 37 | Lp(a) | 37 |
| Extra plasma | 70 | Extra serum | 80 |

Outcomes Data:
The intervention cohorts thus far are showing change in the desired direction for most of the measured coronary artery disease (CAD) risk factors over the initial 12 week period (Table 21A). Lack of statistically significant levels of improvement in some measures may be attributable to small sample size and wide variability in some measures. Results from the first year follow up time point are show in Table 14B. No participants have had any breast cancer recurrence or new breast cancer diagnosis for those participants at increased risk. Only one cohort has reached the year 1 time point (Table 21B) and no participants have been enrolled into the control arm of the study.

**Table 21A. Comparison of baseline to Week 12 data for 16 participants in the STEP Program**

| Category / Metrics | N | Average Baseline Value (SD) | Average Week 12 Value (SD) | Average Change | P Value |
|---|---|---|---|---|---|
| **Weight (lbs.)** | 16 | 182.57 (35.9) | 179.30 (33.0) | -3.3 | <0.01 |
| **Body Mass Index** | 16 | 32.83 (6.3) | 32.04 (5.9) | -0.8 | <0.01 |
| **Total Cholesterol (mg/dl)** | 16 | 198.38 (36.4) | 196.69 (44.2) | -1.7 | 0.7954 |
| **High Density Lipids (mg/dl)** | 16 | 54.44 (12.4) | 52.25 (12.8) | -2.2 | 0.0928 |
| **Low Density Lipids (mg/dl)** | 16 | 114.50 (28.7) | 118.63 (38.4) | 4.1 | 0.5290 |
| **Triglycerides (mg/dl)** | 16 | 155.13 (90.6) | 132.81 (73.4) | -22.3 | 0.0926 |
| **Systolic Blood Pressure** | 16 | 134.75 (18.8) | 124.50 (14.1) | -10.3 | 0.0763 |
| **Diastolic Blood Pressure** | 16 | 80.63 (11.3) | 73.75 (8.1) | -6.9 | <0.05 |
| **Depression Scale [CES-D]** | 16 | 15.31 (10.2) | 11.44 (10.4) | -3.9 | 0.0914 |
| **Hostility Scale [Cook-Medley]** | 16 | 7.06 (4.4) | 5.25 (3.3) | -1.8 | 0.0720 |
| **Perceived Stress Scale [PSS]** | 16 | 17.00 (7.2) | 12.88 (6.5) | -4.1 | <0.05 |
| **Daily Total Fat (grams)** | 0 | --- | --- | --- | --- |
| **Daily Saturated Fat (grams)** | 0 | --- | --- | --- | --- |
| **Avg. CCA/Mean IMT** | 16 | 0.735 (0.1488) | 0.810 (0.1677) | 0.075 | <0.01 |
| **Avg. CCA / Max IMT** | 16 | 0.865 (0.1556) | 0.928 (0.2046) | 0.1 | <0.05 |
| **Fasting Glucose (mg/dl)** | 16 | 107 (28.8) | 109 (25.7) | 2.4 | 0.6604 |
| **HgbA1c** | 16 | 6.3 (0.87) | 6.5 (0.77) | 0.2 | 0.3545 |
| **Cortisol** | 16 | 12.8 (3.83) | 16.5 (5.44) | 3.7 | 0.0507 |
| **TSH** | 16 | 1.71 (1.342) | 2.07 (1.674) | 0.4 | 0.2887 |
| **Epworth Sleepiness Scale (0 to 24)** | 16 | 9 (4.5) | 8 (4.2) | -0.9 | 0.4320 |
| **Pittsburgh Sleep Quality Index (0-21)** | 16 | 10 (4.8) | 8 (4.4) | -2.5 | 0.0512 |

**Table 21B. Comparison of baseline to Year 1 data for STEP Cohort #1**

| Category / Metrics | N | Average Baseline Value (SD) | Average Year 1 Value (SD) | Average Change | P Value |
|---|---|---|---|---|---|
| **Weight (lbs.)** | 8 | 181.50 (39.1) | 174.10 (36.7) | -7.4 | 0.1512 |
| **Body Mass Index** | 8 | 31.86 (6.1) | 30.57 (5.7) | -1.3 | 0.1879 |
| **Total Cholesterol (mg/dl)** | 9 | 208.89 (38.7) | 213.78 (41.1) | 4.9 | 0.5757 |
| **High Density Lipids (mg/dl)** | 9 | 53.11 (12.9) | 48.33 (10.3) | -4.8 | <0.01 |
| **Low Density Lipids (mg/dl)** | 9 | 122.11 (30.0) | 134.33 (36.2) | 12.2 | 0.0919 |
| **Triglycerides (mg/dl)** | 9 | 182.33 (111.1) | 156.22 (79.1) | -26.1 | 0.1587 |
| **Systolic Blood Pressure** | 9 | 134.44 (23.0) | 132.22 (28.8) | -2.2 | 0.8388 |
| **Diastolic Blood Pressure** | 9 | 81.56 (13.7) | 79.11 (11.7) | -2.4 | 0.5754 |
| **Depression Scale [CES-D]** | 9 | 16.00 (5.7) | 11.11 (6.3) | -4.9 | 0.1072 |
| **Hostility Scale [Cook-Medley]** | 9 | 6.89 (4.2) | 6.00 (4.6) | -0.9 | 0.4468 |
| **Perceived Stress Scale [PSS]** | 9 | 20.44 (3.6) | 13.89 (5.8) | -6.6 | <0.05 |
| **Daily Total Fat (grams)** | 0 | --- | --- | --- | --- |
| **Daily Saturated Fat (grams)** | 0 | --- | --- | --- | --- |
| **Avg. CCA/Mean IMT** | 9 | 0.667 (0.0731) | 0.814 (0.0745) | 0.146 | <0.001 |
| **Avg. CCA / Max IMT** | 9 | 0.800 (0.0917) | 0.925 (0.0818) | 0.1 | <0.01 |
| **Fasting Glucose (mg/dl)** | 9 | 114 (34.9) | 125 (48.5) | 10.2 | 0.1554 |
| **HgbA1c** | 9 | 6.7 (0.87) | 6.4 (0.97) | -0.4 | 0.0896 |
| **Cortisol** | 9 | 13.0 (3.39) | 13.9 (4.58) | 0.9 | 0.6805 |
| **TSH** | 9 | 1.89 (1.625) | 1.93 (1.188) | 0.0 | 0.8679 |
| **Epworth Sleepiness Scale (0 to 24)** | 9 | 9 (5.2) | 8 (5.0) | -0.6 | 0.4676 |
| **Pittsburgh Sleep Quality Index (0-21)** | 9 | 13 (3.1) | 9 (4.3) | -4.1 | <0.01 |

Adverse Events: All adverse events are submitted to and adjudicated by the Windber Medical Center Institutional Review Board and TATRC after review by both the Principal Investigator and Medical Monitor. There have been 2 adverse events, both deemed serious events. A serious event is defined as occurring at any dose or intervention level that results in any of the following outcomes: (1) results in death, (2) a threat to life, (3) inpatient hospitalization or prolongation of existing hospitalization, (4) persistent or significant disability or incapacity, (5) causes cancer, (6) is an overdose, or (7) any medical event that requires treatment to prevent one of the medical outcomes listed above. These 2 events were considered serious due to inpatient hospitalizations. Both were non-cardiac and non-breast cancer related events. No deaths occurred and none of these adverse events were deemed to be study related.

Protein profiling of breast cancer patients with CVD risk factors:
Technology is being developed to assess protein expression differences among breast cancer patients with cardiovascular risk factors. Plasma samples are being selected to reflect different stages of invasive cancer from patients with at least two reported cardiovascular risk factors. Plasma samples will be analyzed for 40 proteins that are believed to be related to breast cancer and/or CVD using xMAP technology and the Luminex instrumentation. The xMAP liquid array technology uses microspheres that are internally dyed with fluorophores. Each microsphere contains a unique signature that can be detected by the Luminex system, allowing many analytes to be multiplexed into the same assay, reducing time and cost for each test. The surface chemistry of the microsphere allows for the coupling of antibodies, oligonucleotides, peptides or receptors,

which are also read by the detection system. The Luminex detection system uses fluidic technology, similar to flow cytometry, which passes the microspheres through a detection chamber where the detection agents are read. The assay design and technology for this project will be used to further study the plasma protein profiles of patients with CVD enrolled in the STEP program.

**Task #9: Continue "Defining the Genetic Basis of Heart Attack and Acute Coronary Syndromes in Military Service Women" (In collaboration with WRAMC ICHP). (Replaced old Task #9 from FY07 SOW and renumbered to Task 12 in FY09 SOW).**

This study will identify genes that affect susceptibility to heart attack in young military service personnel who have had a heart attack before the age of 55. Patients will be selected from the Department of Defense Serum Repository, which has millions of serum samples in storage. Cutting-edge technology will be used to isolate very small amounts of DNA that can be found in serum. The entire genome will then be amplified and 500,000 variations in the DNA will be tested. The ultimate objective is to identify new genes that increase risk for heart attack at an early age – such genes represent new targets for preventive or therapeutic interventions.

**Status:**
Institutional Review Board approval was received from Windber Medical Center on June 27, 2008, but approval has not yet been received from the Institutional Review Board at Walter Reed Army Medical Center or the Army's Office of Research at Fort Detrick.

Based on conversations with Dr. Vernalis at WRAMC, we have revised the study protocol, which will be initiated as a feasibility study. This modification in the study design will determine the feasibility of isolating, amplifying, and genotyping quality DNA from serum samples in the Department of Defense Serum Repository (DoDSR). For this proof-of-principal study we aim to: (1) assess the quantity and quality of DNA isolated from serum samples obtained from the DoDSR, (2) conduct whole-genome amplification of the serum DNA and evaluate the resulting whole-genome amplified DNA (wgaDNA), and (3) evaluate the performance of the obtained wgaDNA on Affymetrix 6.0 SNP arrays containing 1.6 million markers. These preliminary studies will determine if we can use DoDSR wgaDNA on high-density genetic marker arrays for future studies.

The current MI in Young Military Service Members protocol will be implemented as phase II after we demonstrate that the DoDSR samples yield quality DNA for genomic studies. We plan to revise the study to obtain 1000 serum samples from the DoDSR (500 subjects, 500 controls) to examine the genomic influences on heart attack. In addition, we will include military men and women less than 55 years of age who have had a diagnosis of myocardial infarction or other acute coronary syndrome. This study will allow us to identify genomic differences that influence early coronary events. Discovering the underlying causes of early coronary events in young individuals will likely provide important targets for new treatments to improve their care and long-term health.

**Task #10: Continuation of the "Comprehensive Cardiovascular Risk Assessment and Prevention Program (CPP)".**

This program serves as a platform for ongoing translational research activities, a "virtual laboratory" based on scientific findings for the development of best personalized preventive practices. In other words, the platform allows ICHP to gather an expansive number of data points for each patient or subgroup of patients (eventually combined with data at a molecular level) that when leveraged will result in the creation of new tools in technology to define wellness, predict and prevent disease, and empower patients and providers to transform their healthcare.

The CPP platform has a dual purpose and is multifunctional. This platform 1) allows for multiple research protocols to be conducted as it sets the stage for recruitment, enrollment and hypothesis generation, advanced data modeling and simultaneously 2) provides a venue where research findings from these protocols can then be tested, validated and translated into application for clinical practice. Our protocols within the CPP are specifically designed to examine the effects of our military's high op tempo which predisposes our service members to accelerated atherosclerotic risk resulting from high stress, PTSD, depression, sleep insufficiency, overweight, prediabetes and prehypertension among other traditional disease risk factors.

This program was established to address the unique needs of military beneficiaries at risk for CV disease. It includes conventional and novel CV risk profiling (health assessments, labs, markers, wearable monitors) and tailored, personalized behavioral recommendations for primary or secondary prevention by an integrative team of providers comprised of a cardiologist, sleep specialist, nurse practitioners, nutritionists, stress management instructors and exercise physiologists. Validated tools to screen for and measure CV risk are part of this inclusive package. Report cards for the patient and provider as well as email notifications are utilized. The program is an adjunct to the best medical practices provided by their primary care provider. Up to 1000 patients may be enrolled each year. Some of the patients (such as nurses or medical holdovers etc) may be in subgroup programs because of unique needs. The CPP serves as a platform for ongoing translational research activities, a "virtual laboratory" for the development of best preventive practices and for CV educational and marketing materials.

**Status:**

| Year | Total # Appointments | Appts/month | New Patient Appts |
|---|---|---|---|
| 2007 | 1095 | 135 | 75 |
| 2008 | 2132 | 178 | 152 |
| 2009 | 1920 | 160 | 120 |
| 2010 (*1st ten months*) | 1590 | 159 | 95 |

From Oct 2009 - Oct 2010, customer satisfaction surveys continued to average a score of 3.9 out of 4.0, demonstrating high patient satisfaction. These numbers encompassed the enrollment of 95 new patients in the CPP, maintaining stable enrollment from the previous fiscal year.

In 2010, media coverage on scientific research discoveries from ICHP were highlighted by the American College of Chest Physicians with interviews by writers from *Reuters* and *Health Day*.

Abstracts presented this reporting period can be found in Appendix C.

Recent analysis of relevant clinical data shows:

I. To examine the relationship between stress and sleep quality, 66 consecutive graduates (mean age 59.6+11.6, 28 men) reduced their PSS 3.1±5.8 points and improved their PSQI 1.2±2.9 points. Fifty subjects were able to reduce their PSS by a mean of 5.5±4.5 points accompanied by improvements in PSQI (1.9±3.0 points), Lp-PLA2 (41.6±53.8 mg/dL), glucose (2.0±9.1 mg/dL), insulin (2.2±7.0 ug/dL) and HOMA (0.04±1.69). The other 16 subjects showed increases in PSS of 4.3±2.0, $p<0.001$ accompanied by worsening PSQI (0.27±2.49, $p=0.02$), Lp-PLA2 (21.7±65.5, $p=0.02$), glucose (2.8±11.0, $p=0.08$), insulin (1.4±6.1, $p=0.07$) and HOMA (0.49±1.51, $p=0.04$). **It can be concluded that reductions in perceived stress correlate significantly with improvements in sleep quality.**

**Improvements in perceived stress and sleep quality are accompanied by improvements in cardiovascular risk markers including glucose metabolism and lipids. Our findings underscore the importance and value of utilizing stress management techniques as a teachable sleep improvement intervention.**

II. To examine the role of stress in stroke risk, 351 consecutively enrolled subjects: 166 (47%) scored above the median PSS. These high-stress subjects displayed an increased cardiovascular risk profile including elevated BMI (31.1±5.9 vs 29.0±5.9, p=0.001), increased Waist Circumference (101.5±17.4 cm vs 98.2±13.8, p=0.04), glucose (98.1±28.2 mg/dL vs 92.8±14.6, p=0.03) and Lp-PLA2 (strongly associated with stroke risk, 220.6±104.7 ng/mL vs 195.6±67.1, p=0.02). High-stress subjects also demonstrated greater daytime sleepiness (ESS=10.4±5.1 vs 7.8±4.8, p<0.001), greater fatigue (5.4±2.2 vs 3.4±2.4, p<0.001), lower sleep quality (PSQI 8.5±4.4 vs 5.9±4.0, p<0.001) and shorter sleep duration (19 min less/24 hr, p=0.04) with a higher risk for sleep apnea (60% at high risk vs 41%, p=0.003) than their low-stress counterparts. **It can be concluded that assessing stress levels in patients may provide targets for intervention in stroke prevention. High stress is associated with numerous behavioral, biochemical and anthropometric factors that increase stroke risk. Comprehensive stroke risk prevention could benefit from an integrative approach that includes lifestyle behavioral assessment to identify as well as to reduce stroke risk and improve quality of life indicators.**

III. To identify the value of Total Sleep Time (TST) on behavioral and biochemical markers, 478 participants (age 54.1±12.4y, 36% men, 169 Caucasian, 121 African-American, 22 Hispanic, 3 Asian, 12 other, 151 undeclared), Berlin Questionnaire indicated high risk for sleep apnea in 53%. Group TST=6.3±1.3h; Sleep Latency (SL)=23.6±38.4 min; PSQI=7.0±4.3; ESS=8.9±5.0 and Fatigue=4.3±2.5; mean BMI=29.8±5.8; PSS=22.4±8.1. For 108 short sleepers (age 50.0±13.0y), Berlin Questionnaire indicated high risk in 66% of subjects; TST=4.5±0.7h; SL=45.9±69.0 min; PSQI=10.9±3.9; ESS=10.7±5.3 and Fatigue=5.7±2.2; mean BMI=31.3±6.5; PSS=24.9±8.7; and hsCRP=0.44±0.55 mg/L. By contrast, the 175 long sleepers, were older (57.2±11.7y, p<0.001); had lower % of subjects at risk for sleep apnea (42%); slept longer (TST=7.6±0.8h, p<0.001); fell asleep more quickly (SL=15.2±14.3 min, p<0.001); had better sleep quality (PSQI=4.6±3.6, p<0.001); had less daytime sleepiness (ESS=7.2±4.8, p<0.001); and less fatigue (Fatigue=3.3±2.6, p<0.001). Long sleepers also weighed less (BMI=29.1±6.0, p=0.004); experienced lower stress levels (PSS=20.4±7.3, p<0.001); and had lower levels of the inflammatory marker hsCRP (0.32±0.47 mg/L, p=0.05). Importantly, there were no differences in lipids, glucose or HgbA1C between short and long sleepers. **It can be concluded that participants who slept longer showed a better CV risk profile and enjoyed higher quality of life by a number of indicators. Despite a lack of difference in the more traditional risk factors, total sleep time is strongly associated with lower stress, healthier body weight, and lower inflammation. These findings underscore the importance of addressing adequate sleep time as a modifiable risk factor in an integrative program for CV risk reduction.**

IV. To examine the relationship between stress and metabolic states, 24 prediabetic subjects, 12 (50%) scored high on the PSS (mean 29.5±4.9 vs 18.4±3.3). These high-stress subjects demonstrated higher mean insulin (20.6±11.7 vs 10.8±4.2, p<0.01), higher insulin resistance, as demonstrated by HOMA, (5.3±2.9 vs 2.8±1.2, p<0.01) and greater percent body fat (38.8±7.6 vs 30.7±8.5, p<0.02), than their low-stress counterparts. There were no differences in glucose or weight between the two groups at baseline.

| Change at 6 mo | Low stress n=12 | High stress n=12 | p value |
|---|---|---|---|
| PSS | 1.4±8.3 | -14.4±9.3 | <0.01 |
| Insulin (ug/dL) | 3.4±7.7 | -11.8±11.8 | <0.01 |
| CRP (mg/dL) | 0.3±0.41 | -0.2±0.7 | <0.03 |

**We demonstrated that high stress correlates with numerous unhealthy metabolic states which place patients at higher risk for CV disease. Prediabetic patients can significantly improve their CV risk profile by reducing stress. We hypothesize that an integrative lifestyle change program may interrupt the negative sequence of events caused by CRF and potentially provide prediabetic patients an adjunct to their CV risk reduction action plan.**

V. To examine the relationship between sleep and weight loss, 78 consecutive graduates completed ICHP at a mean of 9.4±2.7 mo. Nine subjects had a body mass index (BMI) <25 kg/m$^2$ at enrollment and were excluded from analysis. The other 69 graduates were overweight (mean BMI=31.1±5.0 kg/m$^2$), had a mean age of 59.0±12.7 yrs, included 31 men (45%), and were racially diverse (34 Caucasian, 30 African-American, 4 Hispanic, and 1 Asian). Of these 69 participants, 43 (age 58.2±13.4 yrs, 17 or 40% men) showed mean improvement in PSQI of 3.5±3.1 points along with mean decrease in BMI=0.74±1.3 kg/m$^2$. In contrast, 26 subjects (age 60.5±11.6 yrs, 14 men or 54%) showed worsening PSQI score of 1.2±1.4 points and a limited decrease in BMI=0.09±1.01, p=0.04. **In conclusion, in overweight subjects, improvements in sleep quality correlated with greater weight loss. Global assessment of sleep quality, rather than a focus on TST alone, may clarify the mechanism between sleep and weight loss. Identifying these components of sleep quality also provides targets for therapeutic intervention.**

VI. Focusing on the Active Duty participants, analysis showed that of 14 participants (9 men), average age 27.7 years, 5 had abnormal CIMT. These five soldiers exercised less (524±183 MET-min/week versus 1577±1253, p=0.10), showed more snoring/OSA (60% versus 11%, p=0.05), weighed more (BMI=32.4±5.6 kg/m$^2$ versus 28.8±4.0, p=0.18), had dyslipidemia (100% versus 33%, p=0.01), lower HDL (43.2±11.8 mg/dL versus 55.7±11.4, p=0.08), and lower vitamin D (12.5±4.7 pg/mL versus 20.0±7.9, p=0.08). **In this cohort of young soldiers, subclinical atherosclerosis was prevalent. Reversible risk factors were identified with easily obtained and inexpensive assessment tools. Our experience supports earlier assessment and prevention to conserve the Fighting Force.**

VII. To assess current clinical guidelines regarding subclinical hypothyroidism, 340 consecutive patients, 51 (15%) were excluded for diagnosed thyroid disease or thyroid replacement medication. The remaining 289 patients (165 women) comprised the study set with 111 Caucasian, 89 African-American, 12 Hispanic, 2 Asian and 75 undeclared. There were 10 patients (3.5%) with SCH (6 women, mean TSH 4.74±0.41) and 279 patients with normal thyroid studies (158 women, mean TSH 1.78±0.82). For patients with and without SCH, two sample t-tests showed no differences in BMI, waist circumference, perceived stress levels, or C-reactive protein. Indices of glucose metabolism between groups were not statistically different, including fasting glucose, HbA1c, and HOMA. Compared to normal subjects, patients with SCH showed no differences in sleep habits and symptoms, including sleep latency, sleep duration, habitual snoring, risk for sleep apnea, daytime sleepiness and fatigue. Lipid studies showed no statistical differences in total cholesterol (p=0.55), LDL (p=0.71), HDL (p=0.16), TG (p=0.77), PLA2 (p=0.18) or LPa (p= 0.68). Spearman's rank-

order correlation showed a statistically significant inverse correlation between TSH level and LPa (rho= -0.146, p=0.012) and identified a correlation between TSH level and HDL (rho= 0.146, p=0.013). Framingham risk index was not statistically different between patients with SCH and normals (p=0.33). SCH was not associated with an extensive array of CHD risk factors in our population. **Our findings support following the current endocrinology guidelines, offering thyroid replacement for SCH only when symptoms of hypothyroidism are clinically compelling. In our Nurse Practitioner managed CPP, the diagnosis of SCH does not appear to warrant thyroid replacement therapy for cardiovascular benefit but should be carefully considered for each patient's circumstances.**

VIII. We compared nutritional assessment tools by using multivariate analysis which revealed weak correlation between DHQ and MDS with the relationship defined as MDS=8.5 – 0.32 x SF + .06 x fiber. This model predicted only 26% of the variability in MDS ($r^2$=0.26). There was significant correlation of each component of the DHQ score except whole grains: saturated fat $r_s$= -0.50, p<0.0005; fruits 0.40, p<0.0005; fiber 0.33, p=0.002; vegetables 0.25, p=0.02; and whole grains 0.01, p=0.93.
**The DHQ alone is not adequate for assessment of compliance with Med Diet. A weakness of DHQ is lack of assessment of whole grains. There is value added with MDS to serve as a comprehensive measure of compliance with the Med Diet.**

IX. In examining differences between high gainers (HG, those who gained ≥1 lb/year) and low gainers (LG, those who gained <1 lb/year) were analyzed by t-test.
HG had less total exercise (1022±1107 MET-min/week) than LG (1353±1695 MET-min/week) with a difference of 331 MET-min/week (p=0.05). Paradoxically, HG were younger (53±9 yrs) than LG (62±10 yrs, p<0.001), gained more weight (75±34 lbs vs 25±14 lbs, p<0.001) and body fat (38±9 % vs 30±7 %, p<0.001), and had higher FPG (98±21 mg/dL vs 93±14 mg/dL, p=0.45) and lower HDL (57±18 mg/dL vs 64±21 mg/dL, p=0.004). Despite age, small amounts of exercise per week (the equivalent of 5 days/week of walking 20 min) can result in large differences in weight gain and improved parameters of the cardiovascular profile, such as % body fat, glucose metabolism and cholesterol profile. **These findings suggest that exercise can potentially provide a lifetime investment with dividends in improved weight management and heart health.**

X. To determine the importance of program completion time we compared fast completers to slow completers. At baseline, fast vs slow completers had similar weight (85.3 vs 82.6 kg, p=0.42), %BF (33.5 vs 36.3, p=0.13), WC (97.4 vs 98.4 cm, p=0.72), SAG (23.7 vs 23.1 cm, p=0.78), and IPAQ (1021 vs 850 met-min, p=0.34). At program completion, both groups had lost similar amounts of weight (fast vs slow, -3.7 vs -2.1 kg, p=0.36), %BF (-1.2 vs -1.2, p=0.99), WC (-1.0 vs -3.4 cm, p 0.20) and SAG (-1.8 vs -1.8, p=0.97), and showed similar increases in activity levels (690 vs 440 met-min, p=0.18). Fast and slow completers showed similar improvements in insulin resistance (IR) defined by the homeostatic model assessment (IR/IR reversed, 5/5 = 100% vs 8/10 = 80%, p=0.32) and reversal of pre-diabetes (PD) defined by fasting glucose (PD/PD reversed, 4/8 = 50% vs 12/16 = 75%, p=0.24). **Contrary to expectations, outcome measures were comparable in both groups. The pace at which an individual completes a program does not appear to alter the success rate. Accommodating an individual's timetable may be of benefit for improved completion.**

XI. Manuscripts submitted for publication:

Kashani M, Eliasson A, Vernalis M. Stress is a modifiable risk factor for stroke prevention, *International Journal of Biology of Stress* 2010.

Other progress to date:

- Active Duty subgroups initiated Total Soldier Concept
    - Designed customized process for workshop, appointments, data collection, coaching, follow-up and aggregate report to Senior Enlisted Advisor
    - Designed tracking system for admin staff to follow flow of pts
- Designed new "Empowerment Train" schematic used to guide program flow
- Optimization Initiative (clinical & administrative)
    - Designed new Interactive Educational Workshop
    - Re-established customer service training for Admin staff
    - Designed motivational incentive sequence for patients
    - Tracked productivity of clinical and admin staff with new system
    - Performed 5% chart reviews quarterly- provided recommendations
    - Refined Clinical Review process and data capture of metrics
- Clinical enhancement of adding CIMT on all pts
- Clinical enhancement of adding Coping Survey to all new patients
- Continued mission to create an ultra-personalized CPP by using data modeling
- ICHP Database and Platform Creation: Designed and communicated infrastructure of database to support the conceptual, logical, dimensional aspects of our clinical mission
- Developed a Data Tracking System to unify and consolidate all protocol outcomes and metrics

Our alumni continue to validate our successful model of care while they return for visits to the CPP/ ICHP to take part in our Healthy Cooking Demonstrations using our *Healthy Cooking Guide* designed to provide Active Duty with practical tips for healthy living.

**Sub Task #10.1 Continue "Validation of the ICHP Cardiovascular Risk Score" protocol.**
Data previously collected on patients enrolled in the Prospective Army Coronary Calcium (PACC) and PACC Rescan projects were reviewed. Specific information was gathered and analyzed to give each patient a CV disease risk score according to a formula developed by the ICHP. This ICHP formula uses the Framingham model of risk prediction and adds historical factors and biochemical markers to produce a novel score predictive of CV disease risk in military beneficiaries. The goal of the study was to validate the utility of this novel ICHP scoring system by comparing the predicted risk with outcomes in this well characterized population. The primary objective of the project was to validate the predictive utility and accuracy of the ICHP CV risk score (or ICHP score). Specifically, the goals: a) to determine if the ICHP score correlates with cross-sectional prevalence of coronary calcium as measured in the PACC project and b) with the development of CHD events such as angina, myocardial infarction, or need for CV intervention such as coronary stenting, angioplasty, or bypass surgery. A third goal: c) to determine the correlation of the ICHP score with coronary calcium progression as measured in the PACC rescan project.

**Status:** After statistical analysis of data from the PACC project, ICHP score performed successfully in the linear model with a coefficient of 0.003 (p=0.004), indicating that an increase of one point in ICHP score was associated with increasing CIMT 0.3%. In the logistic model, the odds

ratio for the ICHP score was 1.04 (p=0.01), signifying that a one point increase in ICHP score increases odds by 4% of having a top quartile "atherosclerosis score".

In conclusion, incorporating novel risk factors such as those proposed in the ICHP score and considering the value of family history may significantly improve the predictive accuracy of CVD risk assessment and may reveal appropriate targets for therapeutic intervention.

Kashani M, Eliasson A, Vernalis M, Wu H, Taylor A. Value of a novel cardiovascular risk score. Published in *Circulation 2*009; 2: e1-e66. (Poster presented at Qual of Care and Outcomes Research in CV Disease and Stroke, Apr 2009).

Further utilized the principles and equations of the ICHP CV Score to analyze new data sets to demonstrate the clinical and practical use of this validated scoring tool as seen in BATTLE Study analysis of patients:

Modlin R, Walizer E, Kashani M, Eliasson A, Vernalis M. Integrative Cardiac Health Project Risk Score Improves Cardiovascular Risk Assessment in Women with Subclinical Atherosclerosis**.** American College of Physicians, Army Chapter, Nov 2010, podium presentation.

To examine our hypothesis that the ICHP Risk Score may improve CV disease risk identification in women, we compared risk prediction using FRS and ICHP Risk Score in a cohort of women with abnormal carotid intima-medial thickness (CIMT) from participants in the BATTLE Study. 128 women underwent clinical and serologic risk factor screening for entry into this lifestyle change intervention study. All had at least 2 CV disease risk factors and subclinical atherosclerosis by CIMT (>75$^{th}$ percentile by age/gender). For this analysis 15 women with diabetes were excluded. FRS and ICHP Risk Score were calculated and compared. Of 113 non-diabetic (mean age=54, range 26 to 81), predominately black (50%) women, 4% smoked, 47% were hypertensive and 81% were dyslipidemic including 27% with low HDL and 33% with LDL>130 mg/dL. Family history of CV disease was positive in 65%. Subjects were obese (mean BMI=32; mean waist circumference=100 cm). Triglycerides were not elevated (mean=109 mg/dL); 50% had hsCRP ≥ 0.3 mg/dL. All subjects were identified as having a low 10-year risk by FRS. When the ICHP Risk Score was applied, 60% shifted from low to medium risk (p<0.0001). **It has been demonstrated that the ICHP Risk Score dramatically improves CV disease risk prediction in this cohort of women with subclinical atherosclerosis. These findings emphasize the need for improved CV disease risk identification in women. Family history and other novel risk factors add predictive value to current risk models and identify potential therapeutic targets.**

Co-authors of initial abstract are collaborating in access to data and manuscript preparation.

**Sub Task #10.2 Continue "Caregivers Optimizing Readiness thru Prevention Strategies" programs (subgroup of CPP).**

This proposal provides a comprehensive health program for the WRAMC nursing staff, including prescriptions for therapeutic lifestyle change.

Project participants complete questionnaires and lab tests to evaluate individual CV risk and identify emotional/behavioral triggers of stress. A dedicated workshop at ICHP delivers comprehensive instruction on diet, exercise, sleep, and stress management. Follow-up over 12 weeks includes facilitated group support sessions, coaching on coping skills, tension tamer techniques, and scheduled group exercise sessions. Participants are engaged by telephone and email to track progress and deliver pertinent instruction and encouragement. At the end of the 12-

week program, measures are repeated to determine progress in stress reduction and changes in the CV health profile. Subsequently, participants continue to be engaged by telehealth and those who report setbacks are offered re-enrollment in the program. Data gathered on participants undergo dynamic statistical modeling to yield predictive information on best lifestyle change strategies to employ for future participants. This dynamic statistical modeling will provide a more precise intervention strategy for incoming participants and allow for improved outcomes, greater efficiencies, and cost savings.

**Status:** Future pilots will be conducted pending funding. The following manuscript published (See Appendix D):
Kashani M, Eliasson A, Chrosniak L, Vernalis M. Taking Aim at Nurse Stress: A call to action. *Milit Med* 2010; 175:96-100.

**Tasks removed from SOW during reporting period:**
**Task #2:** Initiate "A Blood Repository for Analysis of Molecular Changes Associated with Cardiovascular Disease Development" protocol.
**Task #8:** Initiate "A Feasibility Study of the Effect of Exercise Intensity on Visceral Fat" protocol.
**Task #9:** Initiate "Influence of Exercise and Stress Management on the Metabolic Syndrome" protocol.

## Key Research Accomplishments

- Non-Invasive Coronary Artery Disease Reversal" (CADRe) Study Protocol
    - Study completed
    - 1 manuscript published; 1 manuscript submitted for publication

- Non-Invasive Coronary Artery Disease Reversal (CADRe) Follow-Up Study
    - Study completed
    - Data reconciliation and analysis in progress
    - Publication plan in progress

- Better Adherence to Therapeutic Lifestyle Change Efforts (BATTLE) Trial
    - Main Study completed; addendum in progress
    - Data management in progress (includes data entry and data reconciliation)
    - Limited onsite data analyses
    - Publication plan in progress

- Dr. Dean Ornish Program for Reversing Heart Disease protocol
    - Subject enrollment over 25 cohorts is complete – 422 participants were enrolled, 339 participants graduated, 83 participants dropped out
    - Age/gender/disease status matched control group established to compare risk factor changes

- Global Profiling of Gene/Protein Expression and Single Nucleotide Polymorphisms Associated with Coronary Heart Disease Reversal
    - Subject enrollment was 374 – 166 participants in the lifestyle change program, 140 subjects serving as the control group, and 68 participants enrolled in the Sub-study
    - Abstract submitted to the Nutrition, Physical Activity and Metabolism / Cardiovascular Disease Epidemiology and Prevention 2011 Scientific Sessions

- Participation in the Program reduces levels of important biochemical risk factors for CAD, such as insulin, CRP, and leptin (manuscript in progress).
- Fundamental molecular changes were shown to occur in Program participants – changes in gene expression occur at 12 weeks and persist at one year – genes involved function in defense and immune response (manuscript in progress)
- Completed analysis of plasma levels of macrophage migration inhibitory factor (MIF) in collaboration with Yale University on 85 participants and 85 controls; analysis of MIF genotype data is pending
- Initial proteomic studies on Program participants indicate that the expression of a number of plasma proteins is altered during the Program

- Acute Endothelial Dependent Responses to Distinct Macronutrient Challenges Study: A Comparison of Brachial Reactivity Responses to a Low Carbohydrate/High Fat, High Carbohydrate/Low Fat, or an AHA Meal in Subjects at Risk for Coronary Heart Disease
    - Study complete
    - 1 Manuscripts published

- Cardiovascular Prevention Program (CPP):
    - Annual review and update of Minimal Risk Protocol for retrospective review of data submitted to DCI.
    - 12 peer-reviewed publications from the CPP have been generated.
    - Clinical Database blueprint finalized with informatics architects.
    - Integrative approach to prevention strategically emphasized with case-based presentations highlighting synergy of healthy behavior on biological systems

- Caregiver Support Program: Protocol prepared and ready for submission pending grant funding.
    - Manuscript published.

- Validation of the ICHP Cardiovascular Risk Score
    - Primary analysis complete
    - 2 abstracts presented

## Reportable Outcomes

**Manuscripts in Scientific Journals:**

Kashani M, Eliasson A, Chrosniak L, Vernalis M. Taking Aim at Nurse Stress: A call to action. Milit Med 2010; 175:96-100.

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## Conclusions

Unhealthy lifestyle behaviors are linked to the development of CHD, as well as other chronic diseases. Projections based on combined CVD risk factor impact suggest that favorable lifestyle habits could nearly eliminate the development of CHD and substantially decrease CHD morbidity and mortality. We have demonstrated that comprehensive lifestyle interventions are remarkably efficacious in reducing CVD risk factors and, in many cases, are comparable to pharmacological interventions. Future research endeavors from this project will provide new information regarding strategies to improve adoption of healthy lifestyle behaviors, the impact of lifestyle interventions on CVD risk, and the biologic mechanisms through which lifestyle changes exert their influence. Through this research, the DOD has a unique opportunity to identify and address adverse lifestyle behaviors and CVD risk factors early and make cardiovascular health a part of the military culture. A commitment to CV health could prevent cardiac events, reduce the need for costly procedures and hospitalization, improve quality of life and protect the investment of highly trained military personnel.

# Appendix A:

## Task #1 Manuscripts

CE

# Achievement of Heart Health Characteristics Through Participation in an Intensive Lifestyle Change Program (Coronary Artery Disease Reversal Study)

**Debra A. Marshall, MD, Elaine M. Walizer, MSN, and Marina N. Vernalis, DO**


- **PURPOSE:** Lifestyle habits and cardiovascular disease (CVD) risk factors are closely linked. Unfortunately, few individuals meet the goals for cardiovascular health that are recommended in public health initiatives. The purpose of this study was to determine the effect of an intensive lifestyle intervention program on the achievement of a group of recognized heart health characteristics as well as on the reduction of individual CVD risk factors.
- **METHODS:** Of 200 military healthcare beneficiaries with coronary artery disease or CVD risk factors (mean age = 61 years) who entered a 1-year, prospective, cohort, multicomponent lifestyle intervention study (lacto-ovo vegetarian diet, exercise, stress management, group support), 186 subjects enrolled and 144 participated for 1 year.
- **RESULTS:** At 3 months and 1 year compared with baseline, the proportion of subjects meeting 5 recognized heart health characteristics improved ($P < .001$): fiber intake >25 g/d (94% and 72% vs 35%); exercise ≥150 min/wk (79% and 58% vs 31%); low-density lipoprotein cholesterol <100 mg/dL (75% and 63% vs 46%); body mass index <25 kg/m$^2$ (34% and 38% vs 23%); and blood pressure <140/90 mm Hg (84% and 83% vs 69%). At 1 year, more subjects (72% vs 32% at baseline), especially those with intervention adherence above (94%) versus below (58%) the study population median ($P < .0005$), achieved 3 or more of these characteristics.
- **CONCLUSION:** An intensive lifestyle intervention promotes achievement of important heart health characteristics that, if maintained, may substantially reduce CVD events.



KEY WORDS

coronary disease

lifestyle

prevention

risk factors



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Prospective studies attest to lower cardiovascular disease (CVD) morbidity and mortality, lower health costs, and better quality of life in people with low, compared with high, CVD risk profiles.[1–6] In US population studies, the prevalence of low risk ranges between 3% and 20%.[7,8] Adverse lifestyle patterns and CVD risk profiles common in the United States are also reflected in the military healthcare beneficiary population.[9] Coronary heart disease is the leading cause of morbidity and mortality in the middle-aged soldier.[10] The prevalence of tobacco use among military personnel is high at 33% when compared with the *Healthy People 2010* goal of less than 12%. While 70% of active-duty military members participate in

strenuous exercise regularly, 57% were overweight (body mass index [BMI] ≥ 25), which is nearly twice as high as in an age-matched US population.[11] This suggests that unhealthy dietary habits may counter the expected favorable impact of a significantly higher level of physical activity than the general population. The Coronary Artery Disease Reversal (CADRe) study was conducted to determine whether military healthcare beneficiaries with, or at risk for, coronary artery disease (CAD) could improve their coronary risk factors and achieve 5 recognized heart heath characteristics through participation in an intensive lifestyle intervention.

## METHODS

This was a prospective, single-arm study modeled after the Dean Ornish Program for Reversing Heart Disease[12–14] that was conceived to determine the feasibility and efficacy of this specific lifestyle intervention in military healthcare eligible population. Volunteer subjects were self-referred military healthcare beneficiaries (15% active duty, 63% retired, and 22% eligible family members), 31 to 81 years old with CVD risk factors and/or CAD, willing to make comprehensive lifestyle changes for 1 year. This protocol was approved by the Department of Clinical Investigation/Human Use Committee of the Walter Reed Army Medical Center (Washington, DC) and the institutional review board at the Uniformed Services University for the Health Sciences (Bethesda, Maryland).

The study began with a 5-day residential retreat for instruction and initial monitoring of the multicomponent lifestyle change intervention that included ultralow-fat diet (≤10% total energy as fat, 5–10 mg of cholesterol per day, soy and legumes as the protein source, limited nonfat dairy products, 35–50 g of fiber, and ≥5 servings of fruit and vegetables daily), aerobic exercise (≥180 min/wk), and stress management (Hatha yoga poses, deep relaxation, meditation, guided imagery for 60 min/d). The fiber and exercise criterion used for the HHI score are based on recommended public health goals and are less stringent than the study lifestyle change intervention goals. Didactic presentations combined with handouts, demonstrations, and practical exercise taught by subject experts provided subjects with specific lifestyle change components and practical instruction for implementation. Subjects practiced the prescribed lifestyle change during supervised and facilitated sessions of exercise, yoga, group support, and group meals. A psychologist or social worker facilitated all group support sessions.

During the first 3 months (phase I), subjects were on site twice weekly, 4 hours each visit, for supervised exercise and yoga, meals with educational lectures, and group support. During months 3 through 9 (phase II), on-site visits were decreased to once weekly. After 9 months (phase III), the on-site visits were replaced by weekly telephone monitoring by nurse practitioners and subjects were invited, but not required, to continue subject-directed, group support with their entry cohort. Subjects voluntarily provided written informed consent before eligibility screening, which included a complete medical history, physical examination, and graded exercise treadmill testing. Exclusion criteria included high-risk treadmill test results, unstable CAD/revascularization procedure within 3 months of study entry, ejection fraction less than 35%, and symptomatic congestive heart failure with ejection fraction 35% or higher, inability/unwillingness to fully participate in all study intervention components, smoker not currently enrolled in smoking cessation program, or substance abuse, including alcohol, within 3 months of study entry. Subjects were entered into the study in cohorts of 10 to 20 within 3 months of giving informed consent.

## DATA COLLECTION

Outcome variables measured at study entry, 3 months, and 1 year included blood pressure, weight, BMI using a factory-calibrated Tanita Body Composition Analyzer (model TBF-300A; Tokyo, Japan), percent body fat,[15] fitness (peak metabolic equivalent [MET] level achieved on maximal treadmill exercise test), fasting plasma lipids (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]), and inflammatory markers (lipoprotein(a) [Lp(a)], homocysteine, fibrinogen, and high-sensitivity C-reactive protein [CRP]). Plasma lipids such as TC, LDL-C, HDL-C, and TG were directly measured on a COBAS INTEGRA analyzer by using reagents from Roche Diagnostics (Indianapolis, Indiana). C-reactive protein was measured with a high-sensitivity, commercially available immunoturbidimetric assay that uses monoclonal anti-CRP antibodies (Roche COBAS INTEGRA, Switzerland). Plasma fibrinogen was measured by a commercially available assay that uses an electrochemical determination of clotting time (STA-Fibrinogen, Diagnostic Stago, France). Plasma homocysteine was measured with an Equal Diagnostics Homocysteine Reagent kit (Exton, Pennsylvania) on a Roche/P Modular System (Switzerland). Lp(a) was measured by using immunoprecipitation methods (Quest Diagnostics Nichols Institute, Chantilly, Virginia). Nutrient composition was determined at baseline and at the visit closest to

weeks 12 and 52, with 3-day food records that were analyzed with Nutritionist V software (Version 2.2, First DataBank, San Bruno, California). Medications were assessed at baseline, and any changes in medications or dosage were queried on a weekly basis.

Intervention adherence was determined from daily personal adherence logs. Diet adherence was capped at 100% and calculated with a scoring system based on essential elements of the lacto-ovo vegetarian dietary pattern. Exercise and stress management adherence were not capped at 100% but calculated as the percentage of goal achieved (180 and 420 minutes, respectively). Logs from weeks 8 to 12 and weeks 39 to 52 were assessed weekly and used to calculate adherence at 3 months and 1 year.

## STATISTICAL METHODS AND ANALYSIS

Analyses were conducted on the 1-year study completer subjects ($n = 144$) as well as those who completed only the first 3 months ($n = 166$). Comparisons of group differences in baseline demographics (age, gender, race) and CVD risk factor variables (BMI, diabetes, hypertension [HTN], dyslipidemia, documented CAD) were performed with 2-sample $t$ tests (for continuous variables) and $\chi^2$ test (for categorical variables). Changes in continuous outcome variables between baseline and 3 months or 1 year were evaluated by using a dependent groups $t$ test for paired comparisons. Changes from baseline to 3 months and 1 year were evaluated in independent models. The Wilcoxon signed rank test was used for variables that were not normally distributed (CRP, TG). Sample size varied slightly across analyses because of missing data on some variables. Values are reported as mean (SD).

An investigator-developed Heart Health Index (HHI) score (range, 0–5), modeled after several healthy lifestyle index scores,[16,17] was calculated for 1-year study completers, with 1 point given for each criterion met in the 5-component index (fiber intake $> 25$ g/d; exercise $\geq$ 150 min/wk; LDL-C $< 100$ mg/dL; BMI $< 25$ kg/m$^2$; and blood pressure $< 140/90$ mmHg). Scores at 3 months and 1 year were compared with baseline with a paired $t$ test. The change in distribution of subjects meeting criteria for each component across study time points was assessed with McNemar test. McNemar-Bowker test was used to assess the change in distribution of HHI scores between baseline and 3 months and 1 year. The impact of adherence on the distribution of HHI scores was analyzed with $\chi^2$ tests. Because of missing data, this analysis included 140 subjects for the 3-month comparison and 132 subjects for the 1-year comparison. A 2-sided probability value of .05 or less was considered statistically significant. Statistical analyses were performed by using SAS statistical software (Version 8.2; SAS Institute Inc, Cary, North Carolina) and SPSS software (Version 14.0; SPSS Inc, Chicago, Illinois).

## RESULTS

We screened 714 subjects to obtain 13 study cohorts ($n = 200$) between February 2000 and March 2004. The final cohort of subjects completed the 1-year study in April 2005. Of the 200 eligible subjects who provided informed consent, 14 withdrew before receiving the lifestyle intervention. There was a 23% dropout rate after 1 year in those subjects who enrolled or initiated the lifestyle intervention ($n = 186$), with 166 subjects (89%) completing phase I (3 month), 149 subjects completing phase II (9 months), and 144 subjects (77%) completing phase III (1 year) of the yearlong study. Major reasons for nonenrollment and discontinuing study participation were time constraints, relocation away from the study site, and dissatisfaction with specific aspects of the study intervention. The enrolled study population was predominantly retired, white men with chronic CAD and/or CVD risk factors (Table 1). Anginal symptoms were reported by 32% of study entrants. Subjects who dropped out ($n = 42$) were comparable with study completers except that they were younger (57.1 ± 11.1 years; $P = .04$) and a lower proportion were white (67%; $P = .04$), had CAD (48%; $P = .02$), had HTN (52%; $P = .05$), or were dyslipidemic (83%; $P = .01$).

Medication use was relatively stable throughout the study. At baseline, all study completers with HTN were taking antihypertensive medications. Proportion

**Table 1 • DEMOGRAPHICS AND BASELINE CHARACTERISTICS: ENROLLED VERSUS 1-YEAR STUDY COMPLETERS**

| | Enrolled ($n = 186$) | 1-y completers ($n = 144$) | $P$ |
|---|---|---|---|
| Age, y | 59.8 ± 10.1 | 60.6 ± 9.7 | .04 |
| Male, % | 69.9 | 71.5 | .45 |
| White, % | 80.1 | 84.0 | .04 |
| Body mass index, kg/m$^2$ | 29.9 ± 5.9 | 29.8 ± 5.8 | .75 |
| Coronary artery disease, % | 63.4 | 68.1 | .02 |
| Hypertension, % | 65.6 | 69.4 | .05 |
| Diabetes, % | 19.4 | 18.8 | .66 |
| Dyslipidemia, % | 93.5 | 96.5 | .01 |

of medication use (baseline to 1 year) was β-blockers (72%–78%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (58%–70%), and calcium channel blockers (58%–70%). Despite an increase in the proportion of types of medications used at study completion, dose comparisons showed that 49% of study completers with HTN experienced no change, 20% decreased medication dosage, and 31% had an increase in medication use. From baseline to 1 year, medication use in persons with diabetes increased slightly from 85% to 89%. No change or a decrease in glucose-lowering medications were seen in 78% of the diabetic study completers; however, the proportion of insulin-only use decreased from 11% to 7% at study completion, with the use of antihyperglycemic oral agents (67%–78%) and combination therapy (7%–4%) remaining stable. Cholesterol-lowering medication use in study completers with dyslipidemia increased from 84% to 96.5% at 1 year; however, 61% reported no change, 14% a decrease, and 25% an increase in their cholesterol-lowering therapy. Statin therapy remained stable (92.2%–92.3), but the proportion of use increased (baseline to 1 year) for niacin (14.7%–19.7%) and fish oil (12.1%–15.4%).

Adherence to the study intervention (Table 2) was better at 3 months than at 1 year (91% vs 82%). Subjects were most compliant with exercise (goal ≥ 180 min/wk): mean weekly time was 203.4 ± 82.0 minutes at 3 months and 172.4 ± 81.7 minutes at 1 year. Adherence with the lacto-ovo vegetarian dietary pattern was about 90% throughout the study. Subjects did not reach stress management goals (performing a variety of Hatha yoga techniques for 420 min/wk); mean weekly time was 299.6 ± 110.7 minutes at 3 months and 248.1 ± 155.4 minutes at 1 year.

**Table 2 • STUDY INTERVENTION ADHERENCE AT 3 MONTHS AND 1 YEAR[a]**

| | 3 mo (*n* = 166) | 1 y (*n* = 144) |
|---|---|---|
| Exercise (≥180 min/wk), % study goal | 111.1 ± 44.9 | 94.8 ± 44.6 |
| Diet (specified vegan diet elements), % study goal | 91.9 ± 9.8 | 89.5 ± 14.1 |
| Stress management (Hatha yoga), % study goal | 70.0 ± 26.8 | 57.9 ± 37.0 |
| Overall adherence,[b] % | 91.1 ± 22.2 | 81.6 ± 24.2 |

[a]Values are mean ± SD. Other than diet, percentage adherence is not capped at 100%.
[b]For 3 months (*n* = 165); 1 year (*n* = 132).

## BASELINE VARIABLES AND 3-MONTH EFFICACY

At 3 months, there was statistically significant improvement in body composition, fitness, blood pressure, and lipid profiles (Table 3). There was a 6.6% weight loss and an 8.7% decrease in percentage of body fat, and fitness improved by 20%. Blood pressure was well controlled at baseline, but further improvements in systolic (−5.4%) and diastolic (−7.3%) blood pressure were demonstrated. Superimposed on the effect of stable statin therapy in most subjects was significant improvement in both TC and LDL-C, with nearly a 16% mean decline in LDL-C. Triglycerides were unchanged. Similar to previous ultralow-fat diet studies,[11,13,18] HDL-C results did not improve (−11.9%) but were balanced by the improvement in TC (−13.4%), with no change in the TC/HDL ratio. Of the inflammatory markers evaluated, only homocysteine (−1.9%) and fibrinogen (4.7%) changed significantly. The estimated energy consumption and protein intake remained stable, whereas other nutrient composition changed significantly. Subjects reported a baseline low-fat diet and further decreased their dietary fat intake to 8.8% of total energy with adherence to a lacto-ovo vegetarian diet. The proportion of dietary carbohydrate increased substantially, largely through a 160% increase in fiber intake.

## MAJOR OUTCOME VARIABLES IN 1-YEAR STUDY COMPLETERS

One-year study intervention completers had comparable baseline variables and 3-month outcomes with phase I–only completers (Table 4), except for their trend in CRP improvement at 3 months. At 1 year, weight loss was less marked than at 3 months, but still significantly improved from study entry (−5.8%). Reduction in percent body fat (−10%) and fitness continued to improve (24%). Blunting of earlier improvements in blood pressure and lipid profile was also seen, but significant changes from baseline levels remained: systolic (−5%) and diastolic (−4%) blood pressure; TC (−5%), LDL-C (−8%), and HDL-C (−2%). In contrast to 3-month findings, inflammatory markers were significantly improved, CRP (−9%), homocysteine (−9%), and fibrinogen (−3%). Nutritional changes were maintained, although there was an increase in fat intake (9.8% from 8.9%) and small decreases in protein and fiber intake. Enrolled study subjects with angina (*n* = 47) demonstrated a significant decrease in frequency (1.1 ± 1.6 to 0.2 ± 1.0

**Table 3 • MAJOR OUTCOME VARIABLES IN PHASE I 3-MONTH STUDY COMPLETERS**

| | Baseline | 3 mo | Change | *P* |
|---|---|---|---|---|
| Body composition and fitness | | | | |
| Weight, lb (*n* = 165) | 199.9 ± 50.4 | 186.2 ± 45.1 | −13.7 ± 9.8 | <.0001 |
| Body mass index, kg/m$^2$ (*n* = 165) | 30.0 ± 6.1 | 28.0 ± 5.4 | −2.0 ± 1.4 | <.0001 |
| % Body fat (*n* = 162) | 28.1 ± 8.1 | 25.6 ± 7.9 | −2.5 ± 3.0 | <.0001 |
| Metabolic equivalents (*n* = 154) | 9.5 ± 2.9 | 11.0 ± 3.0 | 1.6 ± 1.7 | <.0001 |
| Blood pressure, mmHg (*n* = 166) | | | | |
| Systolic | 128.5 ± 16.3 | 120.7 ± 16.0 | −7.8 ± 16.4 | <.0001 |
| Diastolic | 74.1 ± 9.7 | 67.8 ± 9.0 | −6.2 ± 11.0 | <.0001 |
| Lipids, mg/dL (*n* = 166) | | | | |
| TC | 179.8 ± 41.1 | 153.3 ± 37.1 | −26.5 ± 31.9 | <.0001 |
| LDL-C | 104.8 ± 30.6 | 86.4 ± 25.8 | −18.5 ± 22.0 | <.0001 |
| HDL-C | 49.3 ± 15.9 | 42.2 ± 10.7 | −7.0 ± 9.8 | <.0001 |
| Triglycerides | 156.8 ± 93.7 | 166.1 ± 103.3 | 9.2 ± 91.1 | .193 |
| TC/HDL-C | 3.9 ± 1.1 | 3.8 ± 1.1 | −0.1 ± 0.8 | .127 |
| Inflammatory markers (*n* = 166) | | | | |
| C-reactive protein, mg/L | 3.3 ± 4.2 | 2.9 ± 3.5 | −0.4 ± 3.9 | .184 |
| Homocysteine, µmol/dL | 9.3 ± 2.7 | 8.8 ± 2.6 | −0.5 ± 2.2 | .006 |
| Fibrinogen, mg/dL | 383.6 ± 77.9 | 397.4 ± 85.8 | 13.8 ± 67.4 | .009 |
| Lipoprotein(a), mg/dL | 41.2 ± 46.6 | 42.8 ± 50.5 | 1.6 ± 19.9 | .297 |
| Nutritional values (*n* = 146) | | | | |
| Total kilocalories | 1,705.0 ± 560.1 | 1,699.0 ± 407.8 | 6.0 ± 569.1 | .899 |
| Fat, % | 24.6 ± 9.5 | 8.8 ± 2.5 | −15.7 ± 9.4 | <.0001 |
| Carbohydrate, % | 56.0 ± 11.5 | 73.3 ± 4.8 | 17.3 ± 11.1 | <.0001 |
| Protein, % | 17.6 ± 4.2 | 16.4 ± 3.1 | −1.2 ± 4.5 | .002 |
| Fiber, g/d | 24.0 ± 12.8 | 49.0 ± 17.8 | 25.0 ± 17.1 | <.0001 |

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

episodes per week; $P < .0001$) over the course of the study.

## ACHIEVEMENT OF HEART HEALTH CHARACTERISTICS

Study participation significantly improved achievement of individual HHI score components (Figure 1). Except for blood pressure, fewer than 50% of study subjects met goals for the other 4 HHI score components at study entry. Only 31% of the subjects exercised for at least 150 min/wk, 23% had a BMI less than 25, 35% reported a dietary fiber intake of more than 25 g, and 46% had an LDL-C of lower than 100 mg/dL. After 3 months of study participation, at least 75% of subjects reached goals for fiber intake, exercise, blood pressure, and LDL-C. Although subjects demonstrated significant weight loss, the proportion of subjects able to achieve normal weight criteria was less dramatic, with 34% of subjects meeting this goal at 3 months and 38% at 1 year compared with 23% at study entry. Dietary, exercise, lipid, and blood pressure improvements diminished at 1 year but remained significantly improved from study entry ($P < .005$).

The HHI score at study entry was 2.0 ± 1.2, increased significantly to 3.7 ± 0.9 at 3 months, and improved to 3.1 ± 1.2 at 1 year compared with baseline ($P < .0005$). The distribution of HHI scores at 3 months and 1 year was also significantly improved ($P < .0005$) from study entry (Figure 2). Only 32% of subjects had an HHI score of 3 or more at study entry, with only 3.5% of them having an HHI score of 5. At 3 months and 1 year, an HHI score of 3 or more was achieved by 89.6% and 72.2% of subjects, respectively. All 5 heart health characteristics were met by 17.4% of subjects at 3 months and by 10.4% at 1 year.

Study intervention adherence had a significant impact on the achievement of heart health characteristic goals (Figures 3a and b). At 3 months, the median overall adherence was 92.4%. Subjects reporting greater than median adherence had significantly higher HHI scores than those with less than median adherence ($P < .0005$). An HHI score of 3 or more was achieved by all subjects with greater than median adherence compared with 81.5% of the subjects with less than median adherence. Median overall adherence was lower at 1 year (78.2%). The difference in distribution of HHI scores

**Table 4 • MAJOR OUTCOME VARIABLES IN 1-YEAR STUDY COMPLETERS**

| | Baseline | 3 mo | Change from baseline | *P* | 1 y | Change from baseline | *P* | *P* (3 mo to 1 y) |
|---|---|---|---|---|---|---|---|---|
| Body composition and fitness | | | | | | | | |
| Weight, lb (*n* = 142) | 198.2 ± 48.2 | 184.9 ± 43.2 | −13.3 ± 9.7 | <.0001 | 186.5 ± 48.1 | −11.7 ± 16.7 | <.0001 | .190 |
| Body mass index, kg/m$^2$, (*n* = 142) | 29.8 ± 5.8 | 27.9 ± 5.1 | −2.0 ± 1.4 | <.0001 | 28.0 ± 5.7 | −1.8 ± 2.5 | <.0001 | .255 |
| Body fat, % (*n* = 139) | 27.9 ± 7.9 | 25.3 ± 7.3 | −2.6 ± 2.8 | <.0001 | 25.0 ± 7.5 | −2.9 ± 3.9 | <.0001 | .284 |
| Metabolic equivalents (*n* = 130) | 9.5 ± 2.9 | 11.3 ± 3.0 | 1.7 ± 1.7 | <.0001 | 11.5 ± 3.4 | 2.0 ± 2.2 | <.0001 | .085 |
| Blood pressure, mm Hg (*n* = 142) | | | | | | | | |
| Systolic | 129.4 ± 16.7 | 120.6 ± 16.4 | −8.8 ± 16.7 | <.0001 | 121.7 ± 14.6 | −7.7 ± 17.0 | <.0001 | .419 |
| Diastolic | 74.1 ± 9.8 | 67.9 ± 9.2 | −6.2 ± 11.2 | <.0001 | 70.4 ± 9.1 | −3.7 ± 10.0 | <.0001 | .009 |
| Lipids, mg/dL (*n* = 144) | | | | | | | | |
| TC | 179.5 ± 40.4 | 151.7 ± 37.2 | −27.8 ± 33.2 | <.0001 | 168.9 ± 40.2 | −10.6 ± 31.9 | <.0001 | <.0001 |
| LDL-C | 104.5 ± 29.7 | 85.1 ± 25.3 | −19.3 ± 22.4 | <.0001 | 94.4 ± 28.3 | −10.1 ± 22.6 | <.0001 | <.0001 |
| HDL-C | 49.2 ± 15.5 | 41.8 ± 9.9 | −7.3 ± 10.1 | <.0001 | 47.2 ± 13.1 | −1.9 ± 7.5 | .002 | <.0001 |
| Triglycerides[a] | 161.5 ± 96.1 | 169.1 ± 106.2 | 7.6 ± 94.1 | .150 | 166.8 ± 91.2 | 5.3 ± 77.1 | .106 | .822 |
| TC/HDL-C | 3.8 ± 1.0 | 3.7 ± 1.1 | −0.1 ± 0.8 | .152 | 3.7 ± 1.0 | −0.1 ± 0.8 | .069 | .756 |
| Inflammatory markers | | | | | | | | |
| C-reactive protein,[a] mg/L (*n* = 144) | 3.2 ± 4.0 | 2.9 ± 3.4 | −0.4 ± 3.6 | .057 | 2.4 ± 2.5 | −0.9 ± 3.1 | .0004 | .007 |
| Homocysteine, μmol/dL (*n* = 144) | 9.4 ± 2.7 | 8.9 ± 2.6 | −0.5 ± 2.2 | .004 | 8.4 ± 2.9 | −1.0 ± 2.4 | <.0001 | .023 |
| Fibrinogen, mg/dL (*n* = 143) | 385.5 ± 79.5 | 400.5 ± 89.0 | 15.0 ± 67.9 | .009 | 370.5 ± 74.4 | −15.0 ± 59.9 | .003 | <.0001 |
| Lipoprotein(a), mg/dL (*n* = 143) | 41.5 ± 47.9 | 43.0 ± 52.1 | 1.4 ± 20.6 | .405 | 42.3 ± 46.7 | 0.7 ± 25.2 | .733 | .786 |
| Nutritional values (*n* = 101) | | | | | | | | |
| Total kilocalories | 1,821.0 ± 573.8 | 1,778.6 ± 388.1 | −42.5 ± 587.5 | .469 | 1,753.6 ± 410.1 | −67.5 ± 559.5 | .228 | .454 |
| Fat, % | 23.9 ± 9.1 | 8.9 ± 2.5 | −15.0 ± 8.8 | <.0001 | 9.8 ± 3.0 | −14.1 ± 9.0 | <.0001 | .003 |
| Carbohydrate, % | 57.0 ± 11.1 | 73.4 ± 5.0 | 16.5 ± 10.1 | <.0001 | 72.5 ± 4.9 | 15.6 ± 10.6 | <.0001 | .039 |
| Protein, % | 17.3 ± 3.7 | 16.1 ± 2.9 | −1.2 ± 4.0 | <.004 | 16.0 ± 2.4 | −1.3 ± 3.8 | <.001 | .662 |
| Fiber, g/d | 26.3 ± 13.2 | 51.6 ± 16.6 | 25.3 ± 15.9 | <.0001 | 47.9 ± 15.5 | 21.6 ± 16.1 | <.0001 | .003 |

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.
[a]Wilcoxon signed rank test.

by adherence remained significant ($P < .0005$). Only 57.5% of subjects with less than median adherence had an HHI score of 3 or more at 1 year in contrast to 94.0% of those with greater than median adherence.

## DISCUSSION

Our findings demonstrate that with an intensive primary/secondary prevention program, military healthcare beneficiary population can achieve substantial improvements in body composition, fitness, nutrition, blood pressure, lipids, and inflammatory markers. When comparing dropouts with completers, an intensive lifestyle change program may be more attractive to those individuals who are retired or without the threat of relocation and able to commit sufficient time to all program components or are highly motivated to seek such a program as a result of CVD risk associated with established CAD or dyslipidemic conditions.

With significant changes seen in dietary patterns, fitness, and body weight, it seems that dose of select

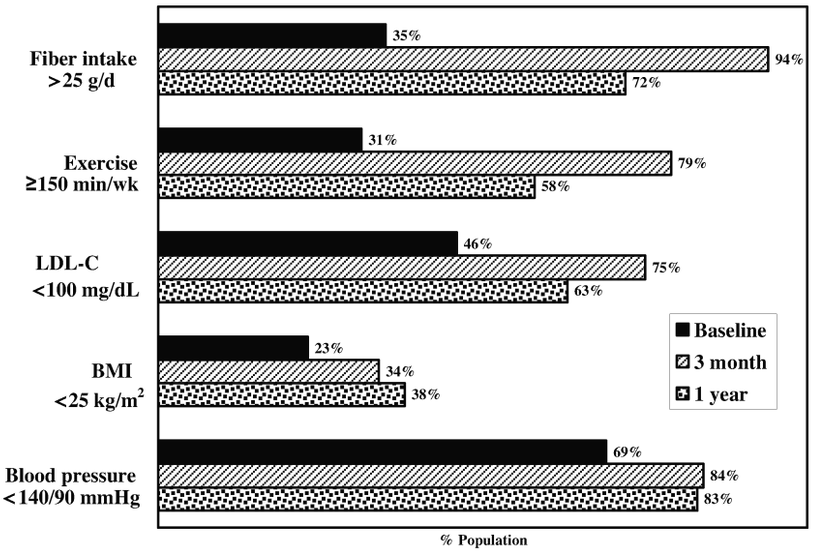



**Figure 1.** Individual heart health characteristics at baseline, 3 months, and 1 year. All changes in distribution are statistically significant at $P < .001$ versus baseline. LDL-C indicates low-density lipoprotein cholesterol; BMI, body mass index.

medications would have been reduced. However, it may be that recent trends for lower lipid and blood pressure goals coupled with the intensive case management to meet evidence-based guidelines provided in the study may have led to fewer reductions in medication dosages as well as improved medication management of HTN, diabetes, and dyslipidemia. Because there were relatively small medication changes throughout the study, this reduction in CVD risk factors, which was seen within 3 months, appears

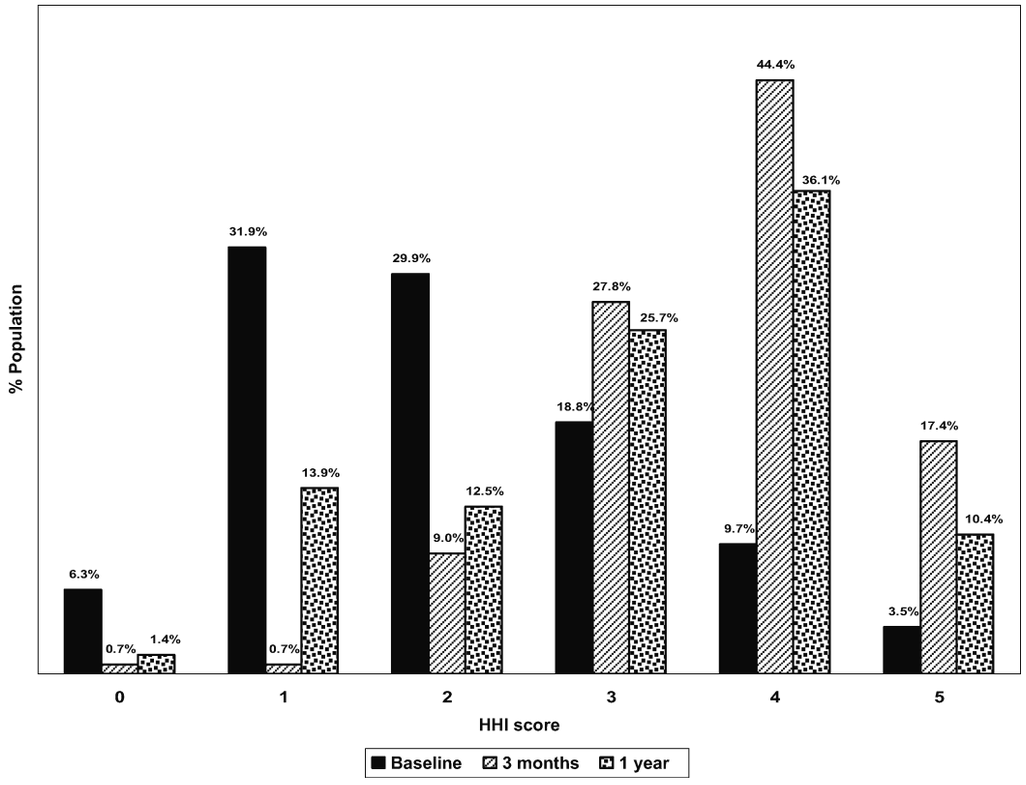
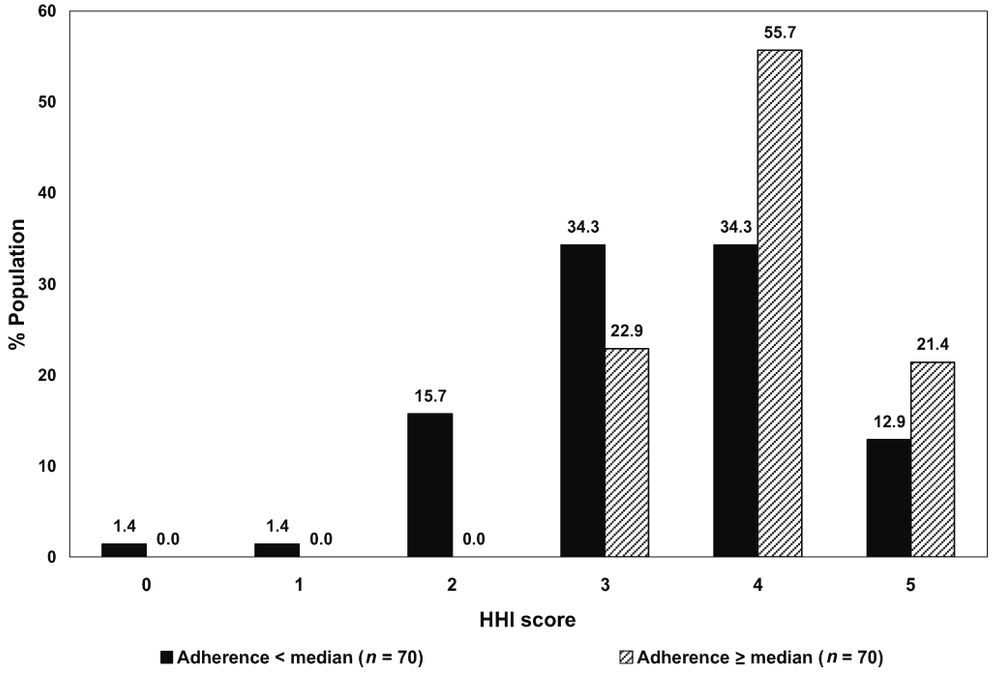
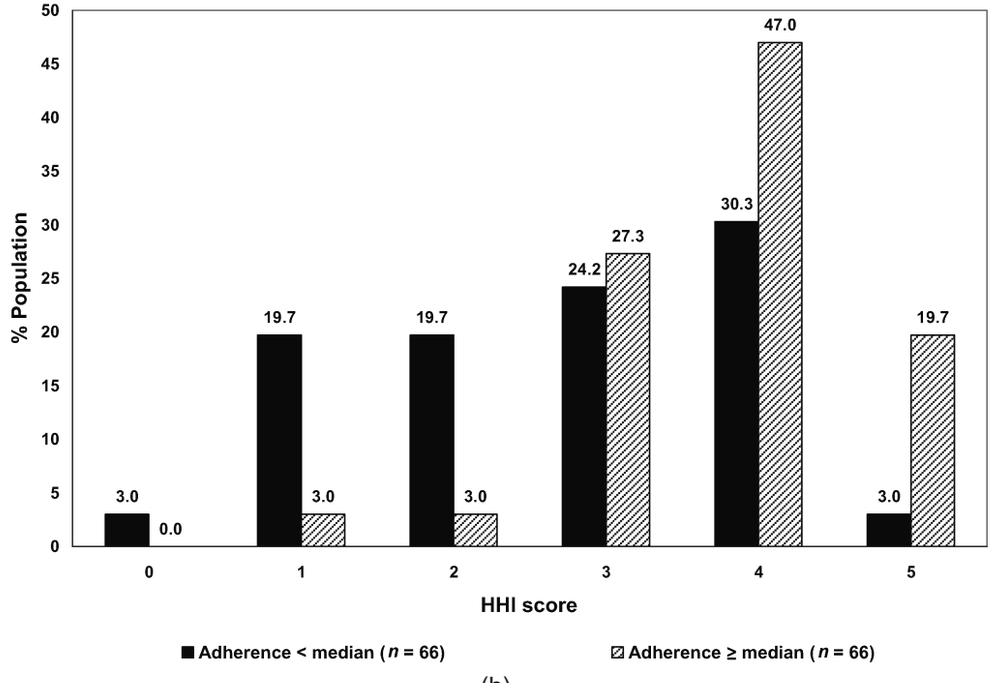



**Figure 2.** Heart Health Index (HHI) scores at baseline, 3 months, and 1 year. Changes in HHI score distribution at baseline versus 3 months or 1 year ($P < .0005$).




(a)




(b)

**Figure 3.** (a) Effect of adherence on Heart Health Index (HHI) scores at 3 months. HHI score distribution between subjects with adherence less than median HHI score versus adherence at or greater than median HHI score ($P < .0005$). (b) Effect of adherence on HHI scores at 1 year. HHI score distribution between subjects with adherence less than median HHI score versus adherence at or greater than median HHI score ($P < .0005$).

to be related to the lifestyle changes effected. The intervention impact diminished by 1 year in the entire study population as the frequency of on-site monitoring decreased. However, those subjects most adherent to the lifestyle changes maintained the improvements in CVD risk factors and heart health goals seen at 3 months.

Considering the intensity of the intervention, the 77% retention rate at 1 year was high, comparable with the Lifestyle Heart Trial (LHT)[12,13] and the Multicenter Lifestyle Demonstration Project (MLDP).[14] Adherence was highest with the exercise component of the intervention, to which the improvements in body composition can be attributed because stable energy intake was reported throughout the study. Subjects who completed the study demonstrated a 2-MET increase in fitness, which may confer a 24% survival benefit according to a study by Myers et al.[19] Improvements in blood pressure, lipids, and inflammatory markers are related to the known effects of exercise and changes in dietary composition, in particular, a reduction in saturated fat intake and an increase in fiber.[16,20–24] Blood pressure and LDL-C reduction have each been shown to reduce CVD events by 23% to 30%.[25] We report similar improvements in weight and blood pressure as the LHT and the MLDP, with a better systolic blood pressure reduction at 1 year (−5% vs −2%). Reductions in LDL-C (−16%) are comparable with those reported in the MLDP at 3 months, but not at 1 year (−8% vs −16%). As in other studies using an ultralow-fat dietary intervention, HDL-C was reduced. While the TC/HDL-C ratio was favorably affected despite HDL-C lowering, we have shown adverse changes in the apolipoprotein profile in a substudy of this population.[26] The clinical significance of both findings remains controversial. Unlike LHT or MLDP, we measured inflammatory markers, which improved during the intervention, except for Lp(a), which is not known to be affected by diet or exercise. While epidemiologic studies linking CVD risk to homocysteine and fibrinogen levels are inconsistent, lower CRP levels have been more consistently associated with reduced CVD risk, although this has not been confirmed in large prospective trials.[27]

We combined 5 of the most common public health recommendations for our HHI analysis.[28] Blood pressure goals were met by most study subjects at baseline (69%) but increased 14% at 1 year and more than 60% achieved an LDL-C under 100 mg/dL. The most substantial gains were realized in meeting diet (using fiber intake as a surrogate for a healthy diet) and exercise goals. The amount of weight lost has been shown in other studies to have health benefits.[29] Target BMI was reached by 15% more of the population than at baseline.

Within 3 months of study participation, nearly 90% subjects achieved 3 or more heart health characteristics, which was also the case at 1 year in the most adherent subjects. A recent review suggested that about a 40% reduction in all-cause mortality might be realized by CAD patients who practice a healthy lifestyle.[22] In the Health Professionals Follow-up Study,[16] men who adopted 2 or more lifestyle practices over 16 years had a 27% lower risk of CAD and 62% of CVD events might have been prevented with the best adherence to recommended lifestyle practices. An 80% lower relative risk for myocardial infarction was found among INTERHEART cohorts who were nonsmokers with healthy diet and exercise habits.[30] The combination of 4 diet and lifestyle factors in the Healthy Ageing: A Longitudinal Study in Europe (HALE) project was associated with a 64% lower rate of CAD death.[31] From these studies, it may be inferred that the 45% of our study population who achieved a 1-year HHI score of 4 or more may realize a significant reduction in CVD events. There are no large longitudinal studies prospectively evaluating the impact of lifestyle changes on hard CVD endpoints. One small study with an intervention similar to ours reported a 10-year CVD event rate of 1.5% in subjects who completed a 2-year lifestyle change program compared with an 18% rate in those who dropped out.[32]

## STUDY LIMITATIONS

Our study is not a randomized trial and thus is subject to the limitations common to all observational studies. The relatively small study size, along with a self-referred, highly motivated, predominantly male, nonsmoking population increases the referral bias. However, the baseline lifestyle behaviors mirror the general population. Additional limitations include lack of 9-month data, self-reported adherence measures, and low screening-to-enrollment rate (26%).

## CONCLUSIONS

Given the observational nature of this study, it is impossible to determine the effect of each program component, what threshold of adherence is necessary, or which intervention components are most important. However, it does appear that frequent on-site monitoring may contribute to sustaining long-term CVD risk factor improvements. Despite major obstacles to the effectiveness of this lifestyle intervention such as the large time commitment to meet program goals and the rigidity of the program

components, adherence to the program goals was remarkable. A 1-year intensive, multicomponent lifestyle intervention is feasible in military healthcare beneficiaries, significantly improves CVD risk factors, and increases achievement of commonly recommended objectives for heart health. Like pharmacologic therapies, promotion and support for long-term maintenance of these favorable heart health characteristics potentially can result in substantial CVD risk reduction.

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# The Effect of a One-Year Lifestyle Intervention Program on Carotid Intima Media Thickness

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Running Title: Marshall; Lifestyle Intervention and CIMT

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## Abstract

### Background

Lifestyle behaviors can reduce cardiovascular (CV) risk factors; however, the impact of lifestyle intervention on atherosclerosis progression is less well established. The purpose of this study was to assess the impact of an intensive, multicomponent lifestyle intervention program on carotid intima media thickness (CIMT).

***Methods and Results***

Common carotid IMT was serially measured with commercial software in 60 subjects (mean age =58.5 ± 9.5), at-risk for or with coronary artery disease (CAD), enrolled in a 1-year prospective, cohort lifestyle intervention study (vegan diet, exercise, stress management, group support). We determined baseline (0.731 ± 0.151 mm) and 1-yr (0.720 ± 0.129 mm) mean CIMT, overall CIMT change and the relationship of CIMT change to the number (0-5) of achieved Heart Health Index (HHI) measures (BMI < 25 $kg/m^2$, exercise ≥ 150 min/wk, BP<140/90 mmHg, LDL Cholesterol (LDL-C) < 100 mg/dL, fiber intake > 25 g/day). Overall CIMT did not change (-0.011 ± 0.118 mm; p= 0.48), however, there was a trend toward CIMT regression (-0.025 ± 0.120 mm vs. +0.033 ± 0.102 mm; p=0.10) between subjects with an HHI Score ≥3 (n=45) compared to those with an HHI Score < 3 (n=15) at study completion.

***Conclusions***

Lifestyle intervention can lead to atherosclerosis regression, but depends on the extent of CV health measures achieved. This finding supports an intensive, case-managed program to fully leverage non-pharmacologic approaches for CV risk reduction.

**Key Words**

Prevention, lifestyle; coronary disease, CIMT

## Introduction

Lifestyle interventions that include a heart-healthy diet, regular physical activity, weight maintenance/reduction, smoking cessation and stress management have been shown to prevent or reduce cardiovascular disease (CVD) risk factors.[1, 2] The efficacy of these non pharmacologic measures can be comparable to pharmacologic therapies, particularly when several health behaviors are adopted together.[3-9]

Large, controlled trials on lifestyle interventions that assess morbidity and mortality endpoints have not been performed due to their expense and difficulties in preventing carryover effects between experimental and control groups during a long-term trial. Therefore, use of surrogate markers that predict the likelihood of CVD events is becoming more accepted as an approach to improve clinical trial efficiency, duration and cost. Measurement of carotid intima media thickness (CIMT) by B-mode ultrasonography is among the imaging tools for noninvasive assessment of atherosclerosis and has been validated as a predictor of cardiovascular events in several studies.[10-13] However, studies assessing the effect of lifestyle interventions on atherosclerosis are limited.

The Coronary Artery Disease Reversal (CADRe) study was conducted in military healthcare beneficiaries, with or at-risk for CAD, to determine the feasibility and efficacy of an intensive, multicomponent lifestyle intervention. This report presents the findings of the CIMT substudy, which assessed the impact of this intervention and the number of CV health measures achieved on atherosclerosis progression over one year.

## Methods

### Study Population and Design

This is a prospective, single-arm study modeled after the Dean Ornish Program for Reversing Heart Disease[8] that was conceived to determine the feasibility and efficacy of this specific lifestyle intervention in a non-residential military population. Volunteer subjects were self-referred military healthcare beneficiaries, age 18 or older with known coronary risk factors or CAD, willing to make comprehensive lifestyle changes for one year. This protocol was approved by the Department of Clinical Investigation / Human Use Committee of the Walter Reed Army Medical Center (Washington, DC) and Institutional Review Board at the Uniformed Services University for the Health Sciences (Bethesda, MD).

The CADRe study has been previously described.[7, 14] Briefly, subjects participated in a 5-day residential retreat for instruction and initial monitoring of the multi-component lifestyle change intervention that included: ultra-low fat diet (≤ 10% total calories as fat, 5-10mg cholesterol/day, soy and legumes as the protein source, limited nonfat dairy products, 35-50 grams of fiber, and ≥ 5 servings of fruit and vegetables daily), aerobic exercise (≥ 180 min/week), and stress management (Hatha yoga poses, deep relaxation, meditation, guided imagery for 60 min/day). During the first 3 months subjects were on-site twice weekly, 4 hours each visit, for supervised exercise and yoga, meals with educational lectures and group support led by a psychologist. During months 3 through 9 on-site visits were decreased to once weekly. After 9 months, the on-site visits were replaced by weekly telephone monitoring by study nurses and

subjects were invited, but not required, to continue subject-directed, group support with their entry cohort.

Subjects voluntarily provided written informed consent before eligibility screening, which included a complete medical history, physical examination and treadmill testing. Exclusion criteria included: high-risk treadmill test, unstable coronary artery disease/revascularization procedure within 3 months of study entry, symptomatic CHF/EF < 35%, inability/unwillingness to fully participate in all study intervention components, or substance abuse, including tobacco, within 3 months of study entry. A total of 714 patients were referred for recruitment between February 2000 and March 2004 from which 200 subjects enrolled and 186 subjects subsequently initiated the lifestyle program in 13 study cohorts. The final cohort completed the one-year study in April 2005. There was a 23% dropout rate after one year in those subjects who enrolled or initiated the lifestyle intervention, with 166 subjects (89%) completing the 3-month milestone and 144 subjects (77%) completing the yearlong study. The major reasons for discontinuing study participation were dissatisfaction with specific aspects of the study intervention, time constraints, and relocation away from the study site. The CIMT substudy began in April 2000. Of 130 subjects with baseline carotid ultrasonography, 93 completed the study. Both baseline and 1-year CIMT measures were available for 60 subjects due to missing or non-interpretable images.

**Data Collection**

**Carotid B-Mode Ultrasound**

Carotid ultrasonography was performed at baseline and 1-year by study nurses and sonographers specifically trained to perform the research study examinations. Images

were obtained on a single ultrasound machine (SonoHeart Elite) using a linear array 5-10 MHz transducer with standardized image settings, including resolution mode, depth of field, gain and transmit focus. All sonograms were obtained with subjects in the supine position and head turned toward the contralateral side. Digital images from a diastolic frame of the cine-loop recording were electronically stored and transferred to an off-line workstation for later analysis. Each ultrasound scan was performed as an independent study, without knowledge of the prior CIMT result, and a subject's prior scan was not used to guide the follow-up examination. A single independent observer, who was blinded to the study phase of image acquisition and trained in the measurement of CIMT, performed the analyses with commercially available software (ProSolv® Echo Analyzer, Problem Solving Concepts, Indianapolis, IN). CIMT was determined from images of the far wall of the distal common carotid arteries (immediately proximal to the carotid bulb) and reported as the mean value for the bilateral measurement. The near (intimal-luminal interface) and far (medial-adventitial interface) field arterial wall borders were manually traced for measurement of mean CIMT (mm) across a 10 mm arterial segment. The high precision and reliability of the ultrasound method and reproducibility of the CIMT measurements (> 0.90 correlation coefficient) have been previously reported.[15]

**Laboratory, Body Composition/Fitness, Blood Pressure and Nutritional Analyses**

Variables measured at baseline and 1-year included: blood pressure by standard auscultatory methods, weight and body mass index (BMI) by a factory-calibrated Tanita Body Composition Analyzer (Model TBF - 300A; Tokyo, Japan), % body fat (3-site skin-fold caliper analysis as described by Pollock[16]), fitness (peak MET level achieved on maximal treadmill exercise test), fasting plasma lipids [total cholesterol, LDL cholesterol

(LDL-C), HDL cholesterol (HDL-C), triglycerides] and high-sensitivity C-Reactive Protein (hsCRP). Total cholesterol, LDL-C, HDL-C, and triglyceride values were directly measured on a COBAS INTEGRA analyzer using reagents from Roche Diagnostics (Indianapolis, IN). CRP was measured with a high-sensitivity, commercially available immunoturbidimetric assay that uses monoclonal anti-CRP antibodies (Roche COBAS INTEGRA, Switzerland). Nutrient composition was determined at baseline and at the visit closest to week 52 with 3-day food records that were analyzed with Nutritionist V software (Version 2.2, First DataBank, San Bruno, CA). Medications were assessed at baseline and any changes in medications or dosage were queried on a weekly basis by study nurses.

**Adherence**

Intervention adherence was determined from daily personal adherence logs. Overall adherence was calculated as the arithmetic average of adherence to each of the intervention components. Diet adherence was capped at 100% and calculated with a scoring system based on essential elements of the vegan dietary pattern (avoidance of meat/poultry/fish and added oils, intake of specified servings of whole grains, fruits, vegetables, legumes, soy protein). Exercise (weekly minutes of structured exercise activity) and stress management (combined weekly minutes of previously described techniques) adherence were not capped at 100%, but calculated as the percentage of goal achieved, which was 180 minutes and 420 minutes, respectively. Logs from weeks 39-52 were used to calculate adherence at 1-year.

### Statistical Methods and Analysis

The 1-year change in mean CIMT across the substudy population (1-year – Baseline CIMT) was evaluated with a paired t-test. A Heart Health Index (HHI) score (range 0-5) was calculated for 1-year completer subjects (*n*=144) with 1 point given for each criteria met in the 5-component index: Fiber intake > 25g/day; exercise ≥ 150 min/week; LDL-cholesterol < 100mg/dL; BMI < 25 kg/m$^2$; blood pressure < 140/90 mm Hg. The effect of the number of CV health measures achieved (HHI Score) on CIMT changes over 1-year was determined using one-way ANOVA for paired comparisons.

Analyses on other continuous outcome variables between baseline and 1-year also utilized a one-way ANOVA for paired or independent comparisons, as appropriate. Fisher's Exact test was used for analyses of non-continuous variables. The Wilcoxon Signed Rank test was used for variables not normally distributed (CRP and triglycerides). Sample size varied slightly across some of these analyses due to missing data on some variables. Values are reported as mean ± SD, except where indicated.

A 2-sided probability value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SAS statistical software version 8.2 (SAS Institute Inc., Cary, NC) and SPSS software (Version 14.0; SPSS Inc., Chicago, IL).

## Results

Subjects were predominantly older Caucasian men with chronic CAD and/or CVD risk factors (Table 1). The CIMT substudy population was comparable to all study completers except that they were slightly younger. Study completers having baseline ultrasonography (n=93) and the CIMT substudy completers also did not differ in their baseline CIMT values. Overall study intervention adherence was approximately 90%.

Exercise and dietary adherence were well maintained at 1-year (≥ 90% study goals) while the time reported for stress management was 57% of goal.

Medication use was relatively stable throughout the study. At baseline, subjects with HTN were taking antihypertensive medications. Proportion of medications use (baseline to 1 year) was β-blocker (70%-73%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (63%-70%). Despite an increase in the proportion of types of medications used at study completion, dose comparisons showed that 50% of subjects with HTN experienced no change, 23% decreased medication dosage, and 28% had an increase in medication use. From baseline to 1 year, medication use in persons with diabetes increased from 80% to 90%. No change or a decrease in glucose-lowering medications were seen in 70% of the diabetic subjects; however, the proportion of combination therapy (insulin plus oral agent use) decreased from 10% to 0% while oral agent use only increased from 70% to 90% of diabetic subjects. Cholesterol-lowering medication use in subjects with dyslipidemia increased from 86% to 88% at 1 year; however, 59% reported no change, 15% a decrease, and 26% an increase in their cholesterol-lowering therapy. Statin therapy slightly increased slightly (76%-79%) as well the use of niacin (14-17%) and fish oil (12%-16%).

Over one year there was significant improvement in body composition, fitness, blood pressure and lipid profiles (Table 2). BMI decreased by nearly 7% and there was a 10% decrease in % Body Fat. Fitness improved 25% as measured by an increase of 2.3 METs. Blood pressure was well controlled at baseline but further improvements in systolic (-4.0%) and diastolic (-3.6%) were demonstrated. On a background of relatively stable lipid medications, a further reduction of 6% occurred in total cholesterol as well as

8% reductions in both LDL-C and triglycerides. The inflammatory marker, CRP, also improved significantly, decreasing by 9%. The estimated energy consumption and protein intake remained stable while other nutrient composition changed significantly. Subjects reported a baseline low-fat diet and maintained dietary fat intake at 10% of total calories with adherence to a vegan diet. The proportion of dietary carbohydrate increased substantially, largely through a 136% increase in fiber intake.

At study entry, less than 55% of study subjects met HHI score components, except for blood pressure (Figure 1). Thirty percent of subjects exercised for at least 150 minutes per week, nearly 77% were overweight and only 35% reported a dietary fiber intake greater than 25 grams. Almost 55% had an LDL-C under 100 mg/dL. After one year of study participation, subjects significantly improved achievement of individual HHI score components. At least 62% of subjects reached the individual index criteria for fiber intake, exercise, blood pressure and LDL-C. Although subjects demonstrated significant weight loss, the proportion of subjects able to achieve BMI in the normal range was less dramatic, with 38% of subjects meeting this goal compared to 23% at study entry. The HHI score at study entry was 2.2 ± 1.4 and improved to 3.3 ± 1.2 by 1-year compared to baseline ($p < 0.0001$). An HHI score ≥ 3 was found in only 38% of subjects at baseline, while at one year 75% achieved this category ($p < 0.0001$). Only 7% of the study population met all 5 HHI criteria at baseline, but improved to 13% at one year.

Given that CIMT values exceeding the 75$^{th}$ percentile for age and gender are generally considered abnormal[17, 18]; 68% of the population (41/60) was abnormal at baseline with a numerical increase to 77% at 1-year that was not significant ($p = 0.20$).

The mean change in CIMT (-0.011 ± 0.118 mm) was also not significant in this population, though there is wide variability seen in the individual CIMT values (Figure 2). Decreases, increases and no change in CIMT were seen in 57%, 43%, and 0% of the population, respectively.

The number of achieved HHI measures correlated with 1-year CIMT change. In subjects with an HHI score ≥ 3 ($n$ = 45) CIMT decreased (-0.025 ± 0.120 mm) compared to an increase (0.033 ± 0.102 mm) in HHI score < 3 ($n$ = 15) subjects ($p$ = 0.10). There was a trend for lower baseline CIMT in the HHI < 3 group (0.682 ± 0.159 mm vs. 0.747 ± 0.147 mm; $p$ = 0.16). Within group comparisons of CIMT change were not significant in the HHI <3 group ($p$ = 0.23) and trended toward significance in the HHI ≥ 3 group ($p$ = 0.16). Of the individual HHI measures (Table 3), the most significant differences between HHI ≥ 3 and < 3 subjects were in LDL-C (-11% vs. +2.1%; p = 0.02), systolic BP (-6% vs. +1.0%; $p$ = 0.04), BMI (-8% vs. -2.6%; $p$ = 0.03) and CRP (-17% vs. +16%; $p$ = 0.03). Within group comparisons HHI measures demonstrated no significant changes from baseline, other than reported exercise time, in the HHI < 3 subjects while all measures, except BMI, improved significantly in the HHI ≥ 3 subjects.

## Discussion

This study demonstrates that military healthcare beneficiaries with chronic CAD or CVD risk factors who fully participate in a multicomponent lifestyle intervention program can realize not only substantial improvement in body composition, fitness, blood pressure, lipids and inflammation, but also an absence of atherosclerosis progression as measured by CIMT, a validated marker of atherosclerosis progression.[19] This finding is likely attributable to the lifestyle intervention as subjects were on relatively stable drug

treatment throughout the study, including lipid-lowering therapies. CIMT did not change significantly for the total study population, despite the overall beneficial changes in CVD risk factors. Only the number of commonly recognized CV health goals achieved, correlating with significant reductions in BMI, blood pressure, LDL-C and CRP, differentiated between those subjects with a trend toward CIMT regression versus progression.

Unlike for pharmacologic therapies[15, 20, 21], there are no large trials that have evaluated the impact of lifestyle interventions on atherosclerosis progression. The Lifestyle Heart Trial, from which the intervention regimen in our study was adapted, used quantitative coronary angiography to demonstrate a 4.5% coronary stenosis improvement in the experimental group compared with a 5.4% worsening in the control group after one year.[8, 9] Although our study had no control group and a small substudy group, the magnitude of CIMT change in the group with the most (-2%) compared to least (+7%) CVD risk factor reduction is similar to that study. More recent studies have assessed the impact of various lifestyle changes on CIMT. Using a similar lifestyle change program to ours, Fields[22] demonstrated a significant CIMT decrease (- 0.15 mm/year) in 20 intervention subjects, although there was no difference between them and subjects in the comparison control groups. When comparing participants in an Ornish lifestyle program ($n$=46) to those in a traditional cardiac rehabilitation program ($n$=47), Aldana[23] was also unable to demonstrate a significant reduction in CIMT. A 6-month diet, exercise and behavior modification program in type 2 diabetics significantly reduced CIMT compared to control subjects (-0.04 mm vs. 0.083).[24] Other studies have reported reduction in CIMT progression,[25] but not regression. Weight loss after bariatric surgery was

associated with three-fold less CIMT progression (0.024 vs. 0.068) compared to obese controls.[26] Reduction of dietary fat intake, along with smoking cessation and BMI decrease of 5 units was associated with a 0.13 mm/year CIMT reduction in progression.[27] In menopausal women, a dietary and physical activity intervention slowed CIMT progression compared to control subjects (0.008 vs 0.004 mm/year), the lower magnitude of effect consistent with a less intense intervention and smaller change in CVD risk factors than seen in our study.[28] CIMT progression was lower in subjects with the greatest vs. least reduction in saturated fat (0.03 vs. 0.10 mm/year).[29] Some lifestyle intervention studies have not demonstrated any effect on CIMT.[30-33] The small study populations as well as the magnitude of CVD risk factor change likely explains the variability of CIMT effect reported. Lipid improvement is an important factor, as the extent of CIMT change has been significantly related to LDC-C changes in pharmacologic studies.[34]

There is potential for lifestyle change to have a favorable impact morbidity and mortality. A recent review suggests that about a 40% reduction in all-cause mortality might be realized by CAD patients who practice a healthy lifestyle.[35] In The Health Professionals Follow-up Study, men who adopted $\geq 2$ lifestyle practices over 16 years had a 27% lower risk of CAD and 62% of their CV events might have been prevented with the best adherence to recommended lifestyle practices.[36] Individuals achieving four diet and lifestyle factors in the HALE project had a 64% lower rate of CAD death.[37] Large-scale epidemiologic studies have found a significant association between CIMT progression and CV events. The Rotterdam Study, Cardiovascular Health Study and The Atherosclerosis Risk in Communities Study demonstrated 1.3 - 1.7 fold higher risk of

myocardial infarction (MI) for approximately each 0.2 mm CIMT increase.[10, 13, 38] Prospective data from the Carotid Atherosclerosis Progression Study (CAPS) confirms these prior findings across a wide age range.[12] In CAPS, each 0.16 mm CIMT increase was significantly predictive of a 1.45 fold higher incidence of MI, stroke or death. Thus, the reduction of CIMT among subjects achieving the greatest number of CV health measures in our study supports the potential of lifestyle intervention to reduce future CV morbidity and mortality. Larger clinical trials of lifestyle interventions that assess CIMT as an endpoint are needed to provide convincing evidence in this regard. In the interim, our findings may be utilized to motivate better adherence in lifestyle change programs to maximize their benefit.

**Study limitations**

Our study is not a randomized trial and, thus, is subject to the limitations common to all observational studies. The highly motivated, predominantly male, nonsmoking population increases the referral bias. The relationships analyzed between CV risk factor changes and CIMT progression were performed in a smaller subgroup, thus adding to bias or confounding from unmeasured factors.

**Conclusions**

Lifestyle intervention can lead to a delay in atherosclerosis progression, but may depend on the extent of CV health measures achieved. This finding supports an intensive, case-managed program to fully leverage non-pharmacologic approaches for CV risk reduction.

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## Figure Legends

Figure 1 Individual Heart Health Characteristics at Baseline and 1-Year

Changes in distribution for fiber, exercise and BMI are statistically significant at $p < 0.004$ vs. baseline

Figure 2 CIMT at Baseline and 1-Year

Changes in individual subjects are shown with group means ±SD

Figure 3 Baseline to 1-Year CIMT Change: Comparison between HHI $\geq 3$ and HHI $< 3$ Subjects

## Tables

**Table 1. Demographics, Baseline Characteristics and Study Intervention Adherence: CIMT vs. All 1-Year Completer Subjects**

| | CIMT Subjects (n=60) | All 1-Year Completers (n=144) | P |
|---|---|---|---|
| Age (years) | 58.6 ± 9.5 | 60.6 ± 9.7 | 0.03 |
| Female (%) | 21.7 | 28.5 | 0.14 |
| Caucasian (%) | 81.7 | 84.0 | 0.88 |
| BMI ($kg/m^2$) | 30.3 ± 5.7 | 29.8 ± 5.8 | 0.39 |
| CAD (%) | 60.0 | 68.1 | 0.10 |
| HTN (%) | 65.0 | 67.4 | 0.72 |
| Diabetes (%) | 15.0 | 18.1 | 0.51 |
| Hyperlipidemia (%) | 96.7 | 95.8 | 1.00 |
| Baseline CIMT (mm) | 0.731 ± 0.151 | 0.729 ± 0.159* | 0.94 |
| Adherence (Overall, %)** | 91.9 ± 20.6 | 92.4 ± 22.0 | 0.88 |
| Diet (% specified pattern)** | 90.5 ± 9.8 | 89.5 ± 14.1 | 0.61 |
| Exercise (% time ≥ 150 min/wk) | 95.4 ± 35.5 | 94.8 ± 44.6 | 0.93 |
| Yoga (% time ≥ 420 min/wk) | 50.7 ± 27.1 | 57.9 ± 37.0 | 0.18 |

*n = 93 for completers with baseline CIMT

** n=143 for All 1-Year Completers due to missing dietary records

**Table 2.**
**Serology, Body Composition/Fitness, Blood Pressure and Nutrition in CIMT Population**

| | Baseline | 1-Year | Change | P |
|---|---|---|---|---|
| **Body Composition & Fitness (n=60)** | | | | |
| Weight (lbs) | 204.5 ± 45.1 | 190.6 ± 45.4 | -14.0 ± 18.9 | <0.0001 |
| BMI ($kg/m^2$) | 30.3 ± 5.7 | 28.2 ± 5.7 | -2.1 ± 2.8 | <0.0001 |
| % Body Fat | 27.3 ± 7.5 | 24.8 ± 7.9 | -2.6 ± 3.3 | <0.0001 |
| MET Level | 9.7 ± 2.7 | 12.0 ± 3.6 | 2.3 ± 2.1 | <0.0001 |
| **Blood Pressure (n=60)** | | | | |
| Systolic (mmHg) | 125.6 ± 14.5 | 120.4 ± 14.6 | -5.1 ± 14.4 | 0.007 |
| Diastolic (mmHg) | 73.2 ± 10.2 | 70.1 ± 9.5 | -3.2 ± 9.8 | 0.015 |
| **Serology (n= 60)** | | | | |
| Total Cholesterol (mg/dL) | 170.9 ± 40.0 | 159.7 ± 37.9 | -11.2 ± 25.2 | 0.001 |
| LDL-Cholesterol (mg/dL) | 98.2 ± 29.0 | 89.2 ± 27.2 | -9.0 ± 21.8 | 0.002 |
| HDL-Cholesterol (mg/dL) | 48.3 ± 12.9 | 47.3 ± 11.8 | -1.0 ± 6.8 | 0.256 |
| Triglycerides (mg/dL) | 147.0 ± 90.5 | 143.1 ± 67.8 | -3.8 ± 67.8 | 0.506 |
| C-Reactive Protein (mg/L) | 3.4 ± 4.2 | 2.3 ± 2.5 | -1.1 ± 3.4 | 0.003 |
| **Nutritional Values (n=44)** | | | | |
| Total Kcal | 1919.6 ± 488.2 | 1780.6 ± 388.4 | -139.0 ± 554.9 | 0.104 |
| % Fat | 25.2 ± 9.6 | 10.1 ± 2.6 | -15.2 ± 9.7 | <0.0001 |
| % Carbohydrate | 55.5 ± 12.0 | 71.9 ± 5.2 | 16.4 ± 11.6 | <0.0001 |
| % Protein | 17.1 ± 3.8 | 15.9 ± 2.6 | -1.2 ± 3.8 | 0.043 |
| Fiber (g/day) | 26.1 ± 11.9 | 51.2 ± 15.0 | 25.1 ± 17.2 | <0.0001 |

**Table 3.**
**Individual HHI Measures and CRP: Comparison between HHI ≥ 3 and HHI < 3 Subjects**

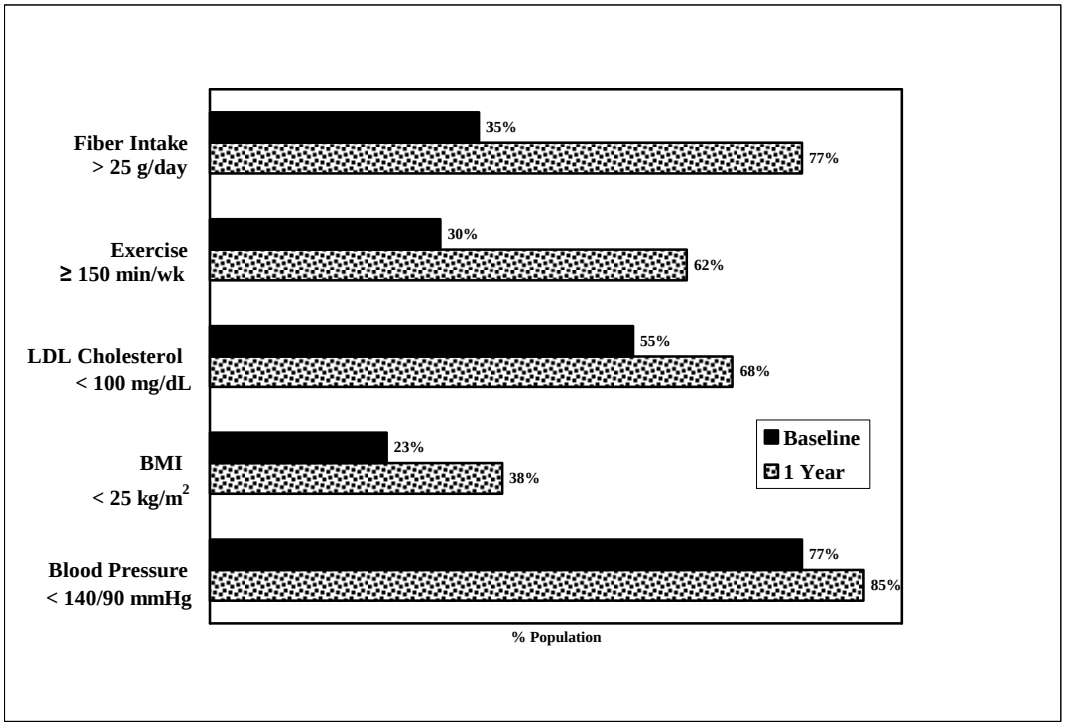
**(% Change from Baseline to 1-Year)**

| | **HHI < 3 Group (n= 15)** | **HHI ≥ 3 Group (n= 45)** | **Between Group, p** |
|---|---|---|---|
| **Body Mass Index** | -2.6 ± 13.2 | -8.2 ± 5.9* | 0.028 |
| **Exercise** | 397.2 ± 183.8* | 415.6 ± 235.0* | 0.816 |
| **Blood Pressure**<br>**Systolic**<br>**Diastolic** | <br>1.0 ± 10.6<br>1.2 ± 14.6 | <br>-5.7 ± 10.3*<br>-5.3 ± 12.1* | <br>0.036<br>0.093 |
| **LDL Cholesterol** | 2.1 ± 25.9 | -11.0 ± 14.8* | 0.019 |
| **Dietary Fiber Intake** | 55.9 ± 45.8 | 142.1 ± 127.3* | 0.254 |
| **C-Reactive Protein** | 16.0 ± 70.5 | -17.2 ± 39.8* | 0.027 |

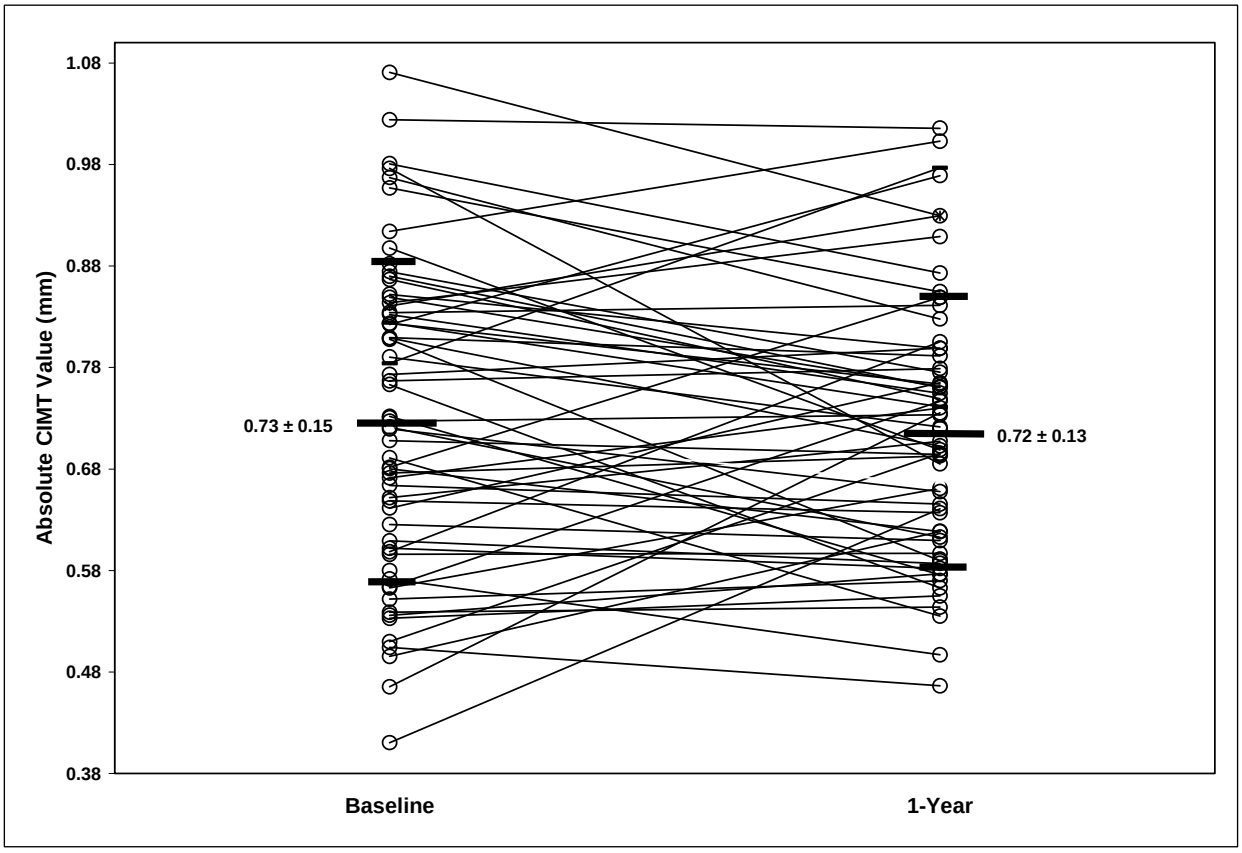
***Within group p < 0.01**

# Figures

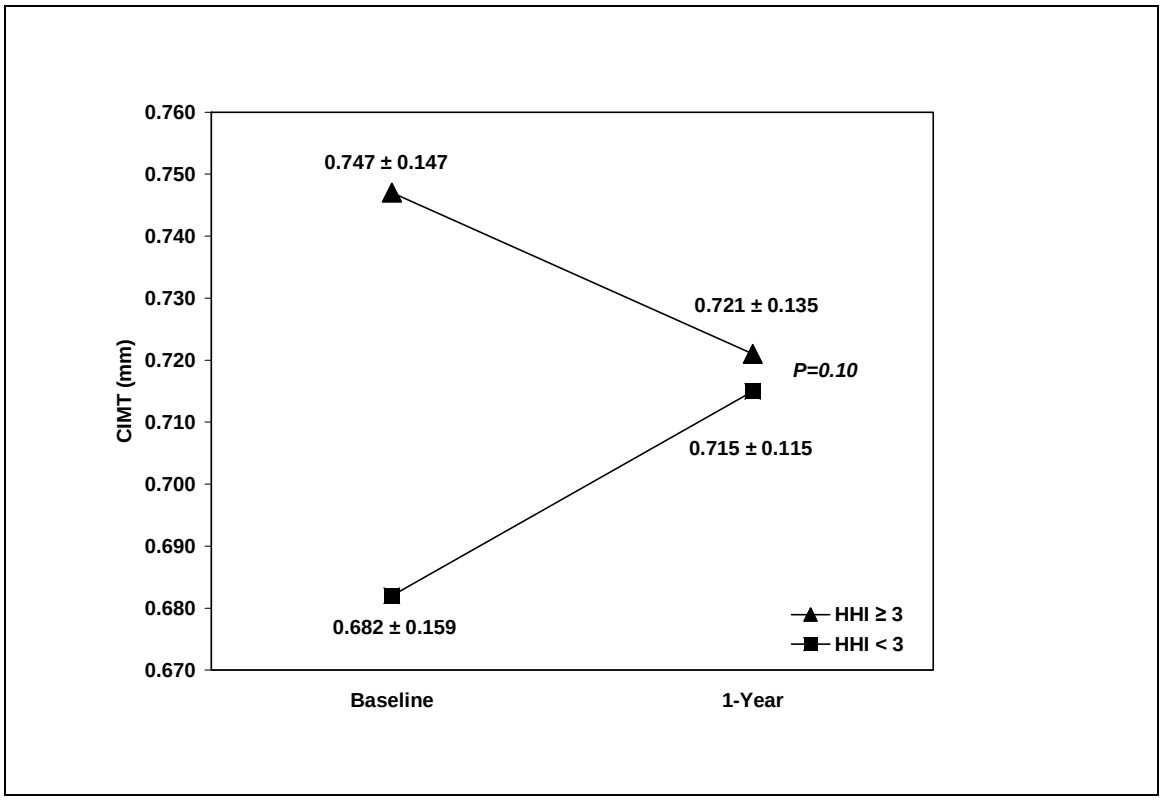
## Figure 1



## Figure 2


1.08
0.98
0.88
0.78
0.68
0.58
0.48
0.38
Absolute CIMT Value (mm)
0.73 ± 0.15
0.72 ± 0.13
Baseline
1-Year

## Figure 3


0.760
0.750
0.740
0.730
0.720
0.710
0.700
0.690
0.680
0.670
CIMT (mm)
0.747 ± 0.147
0.721 ± 0.135
P=0.10
0.715 ± 0.115
0.682 ± 0.159
HHI ≥ 3
HHI < 3
Baseline
1-Year

# Appendix B:

## Task #7 Manuscripts

American Dietetic Association

RESEARCH

Research and Professional Briefs

# Comparative Effects of Three Popular Diets on Lipids, Endothelial Function, and C-Reactive Protein during Weight Maintenance

MICHAEL MILLER, MD; VALERIE BEACH, RN; JOHN D. SORKIN, MD, PhD; CHARLES MANGANO, RDMS; CHRISTINE DOBMEIER, RD; DANICA NOVACIC, MD; JEFFREY RHYNE, MS; ROBERT A. VOGEL, MD

**ABSTRACT**

Although popular diets focus on weight loss and their favorable biochemical and physiological effects, fewer investigations have evaluated the biological impact of these diets during weight maintenance. To study this issue, three popular diets—Atkins, South Beach, and Ornish—were tested in a randomized and counterbalanced crossover study between January and December 2006. Participants completed each of the three 4-week isocaloric dietary intervention phases followed by a 4-week washout period. They were weighed weekly and caloric adjustments made if weight change exceeded 1 kg. At the completion of each dietary phase, 3-day food records were analyzed, fasting blood sampled, and brachial artery reactivity testing performed. Eighteen adults completed all three isocaloric dietary phases. During the South Beach and Ornish maintenance phase, there were significant reductions in low-density lipoprotein cholesterol (11.8%; $P=0.01$, 16.6%; $P=0.0006$, respectively) compared to prediet baseline. In addition, in contrast to the Atkins maintenance phase, significant reductions in low-density lipoprotein cholesterol and apolipoprotein B levels were observed after the South Beach ($P=0.003$, $P=0.05$; repeated measures analyses of variance) and Ornish maintenance phases ($P=0.0004$, $P=0.006$, repeated measures analyses of variance). Brachial artery testing revealed an inverse correlation between flow-mediated vasodilatation and intake of saturated fat ($r=-0.33$; $P=0.016$). These data suggest that during weight maintenance, less favorable biological effects are observed during a simulated, high-fat Atkins diet when compared to the South Beach and Ornish diet. The findings support additional study in subjects with visceral obesity and the metabolic syndrome, in whom an increased risk of coronary disease at baseline may be accentuated with chronic consumption of a diet that exhibits unfavorable effects on lipids and endothelial function.

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Popular diets designed to induce acute weight reduction represent a multibillion dollar a year industry (1). While numerous studies have evaluated the effectiveness of weight reduction and the extent to which weight loss is associated with improvement in a variety of metabolic parameters (eg, glucose, lipids, blood pressure), considerably less information is available with regard to the effect of these parameters during weight maintenance. This is an important area to investigate because weight maintenance often represents the chronic phase prescribed after acute weight reduction has been achieved. Yet, surprisingly few data are available in the assessment of popular diets during weight maintenance. Because coronary heart disease (CHD) remains the leading cause of death in the United States and dietary factors contribute to development and acceleration of atherothrombosis (2), the present study was designed to evaluate the impact of biochemical and physiological parameters affecting CHD risk during weight maintenance. If saturated fat is associated with low-density lipoprotein (LDL) receptor downregulation (3) and endothelial dysfunction (4), two potential mechanisms accounting for elevated CHD risk (5), then popular diets that advocate high saturated fat intake (ie, Atkins) may exhibit unfavorable effects on lipids and endothelial function compared to lower saturated fat intake during the weight-maintenance phase.

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## METHODS

### Subjects

A total of 26 adults responded to a posted advertisement seeking healthy adults aged 20 years and older. Because the study was not designed to investigate weight loss, inclusion criteria consisted of body mass index (calculated as $kg/m^2$) <30 and with no history of metabolic, hepatic, renal, or systemic disease. They were comprised predominantly of medical students, residents, and hospital employees. Participants were asked not to use herbal remedies, fish oils, or anti-inflammatory medications. Alcohol use was permitted provided that intake was regular and that no more than 1 ounce was consumed daily. None of the volunteers were taking lipid-lowering or antihypertensive agents. Patients taking vasoactive medications (eg, cetrizine) were asked not to take the medication the evening prior to brachial artery reactivity testing. Volunteers were asked to maintain the same level of physical activity throughout the study. All studies were performed after an overnight fast of at least 12 hours, which included restriction of caffeine and alcohol. The protocol was approved by the Institutional Review Board and all subjects provided written informed consent.

### Study Methods

This was a randomized crossover study of three 4-week dietary interventions with a 4-week washout period after each dietary phase for a total study period of 6 months for each participant. At the end of each 4-week interval, subjects returned for fasting blood measurements and brachial artery reactivity testing. The study was undertaken between January and December 2006.

### Dietary Phases

Outpatient dietary interventions were based on three popular diets, the high-fat, low-carbohydrate Atkins diet (6), the Mediterranean South Beach diet (7), and the high-carbohydrate, low-fat Ornish diet (8). Dietary assignment was randomized and counterbalanced. At baseline, each volunteer provided 72-hour food records for analysis by a registered dietitian (RD), which served as the template for teaching participants how to record food items and quantity consumed during the trial. Subjects were informed at the outset that the study was not aimed at weight reduction but rather weight maintenance (eg, within 1% to 2% of body weight) throughout the 6-month trial. Therefore, volunteers were weighed at weekly intervals and, if weight alterations exceeded 1 kg, the RD adjusted caloric and nutrient intake accordingly. A total of six volunteers had dietary adjustments made during their 4-week dietary phase in order to maintain their weight within the designated range. At the conclusion of each 4-week dietary phase and 4-week washout phase, subjects presented after a 12-hour fast for blood drawing and endothelial testing. In all, there were six different phases: first diet, washout, second diet, washout, third diet, and washout, for a total of 24 weeks from first diet to study completion.

### Laboratory Methods

**Lipoprotein and Biochemical Analysis.** Following an overnight fast and signed consent, 30 mL blood was collected by venipuncture into two tubes containing ethylene diamine tetraacetic acid centrifuged within 30 minutes at 4°C to separate plasma. Total cholesterol and triglycerides were measured using a Hitachi 704 clinical chemistry analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) and high-density lipoprotein (HDL) cholesterol was measured following precipitation of apolipoprotein B–containing lipoproteins as described previously (9). Apolipoproteins A-I and B were measured using a nephelometer (Behring Diagnostics, Inc, Westwood, MA) with reagents supplied by the manufacturer. Electrolytes, hepatic function, and high-sensitivity C-reactive protein were measured by Quest Diagnostics (Van Nuys, CA).

**Brachial Artery Flow-Mediated Vasodilation.** Brachial artery flow-mediated (endothelial-dependent) vasodilation (FMD) was measured using an 11-5 MHz broadband linear-array transducer and baseline images were acquired after a 15-minute supine equilibration period as described previously (10). Poststimulus images were acquired 1 minute$\pm$15 seconds following release of a 5-minute upper-arm occlusion. Baseline measurements were performed prior to each 4-week dietary phase and represented the average of three measurements that were analyzed by an experienced investigator blinded to subject's identity and study phase.

### Statistics

Sample-size calculations determined that 18 subjects would be required to detect a 15% reduction in total cholesterol between the high- and low-fat dietary phases, with a standard deviation of 27 mg/dL, power 90%, and $\alpha$=0.05. Following each dietary phase, 72-hour food records were analyzed by an RD (C.D.) using the Nutri Base V Personal Plus edition (version 5.19, 2005, Cyber-Soft, Inc, Phoenix, AZ). Participants were asked to record the amount of each item consumed; one RD reviewed the food records for completion and a second RD checked all entries to verify accuracy. Differences in energy intake, lipids (including log transformation for triglyceride analysis), lipoproteins, and other biochemical measurements before and after each dietary phase were analyzed using STATA Statistical Data Analysis software (version 8.2, January 2003, StataCorp, College Station, TX) and SAS (version 9.13, 2005, SAS Institute, Cary, NC). Repeated measures analyses of variance (SAS proc Mixed, with a repeated statement and compound symmetric covariance structure) was used to estimate the mean within-person (post-prevalue) change and standard error of the within-person changes in metabolic parameters. A two-tailed $P \leq 0.05$ was considered significant. For the brachial artery studies, FMD was quantified as the percent diameter change of the postocclusion arterial diameter measurement relative to baseline and end-diastolic frames. Pearson's correlation analysis was used to evaluate the association of change between saturated fat intake and FMD.

## RESULTS AND DISCUSSION

Of 26 participants who enrolled in the study, 18 (nine men and nine women) completed the study; eight with-

**Table.** The effect of three popular diets on lipids, lipoproteins, apolipoproteins A-I and B (mg/dL), and C-reactive protein (mg/L) before and after completion of each 4-week dietary phase of the crossover study[ab]

| | | | | | *P* Value | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Between Diets[g] | | |
| | Pre[c](SD[d]) | Changes | SE[e] | 95% CI[f] | | AS | AO | SO |
| **TC**[h] | | | | | | 0.007 | <0.0001 | 0.06 |
| Atkins | 183.8 (44.0) | 9.2 | 4.7 | 0.0 to 18.3 | 0.06 | | | |
| South Beach | 182.6 (47.6) | −9.8 | 4.7 | −19.0 to 0.7 | 0.04 | | | |
| Ornish | 191.7 (51.2) | −22.7 | 4.7 | −31.8 to −13.5 | <0.001 | | | |
| **TG**[i] | | | | | | 0.95 | 0.08 | 0.07 |
| Atkins | 83.3 (29.7) | −3.7 | 7.9 | −19.1 to 11.8 | 0.65 | | | |
| South Beach | 94.9 (47.6) | −4.3 | 7.9 | −19.8 to 11.1 | 0.59 | | | |
| Ornish | 86.1 (41.3) | 16.2 | 7.9 | 0.7 to 31.6 | 0.048 | | | |
| **TG**[j] | | | | | | 0.56 | 0.03 | 0.10 |
| Atkins | 4.37 (0.34) | −0.08 | 0.08 | −0.23 to 0.08 | 0.35 | | | |
| South Beach | 4.44 (0.50) | −0.01 | 0.08 | −0.16 to 0.15 | 0.91 | | | |
| Ornish | 4.35 (0.47) | 0.18 | 0.08 | 0.02 to 0.33 | 0.03 | | | |
| **HDL**[k] | | | | | | 0.98 | 0.01 | 0.01 |
| Atkins | 62.9 (18.0) | 1.2 | 2.6 | −3.9 to 6.4 | 0.64 | | | |
| South Beach | 62.0 (15.3) | 1.1 | 2.6 | −4.0 to 6.3 | 0.67 | | | |
| Ornish | 64.3 (14.7) | −8.7 | 2.6 | −3.6 to 13.9 | 0.002 | | | |
| **LDL**[l] | | | | | | 0.003 | 0.0004 | 0.44 |
| Atkins | 96.1 (24.8) | 8.1 | 4.4 | −0.4 to 16.7 | 0.07 | | | |
| South Beach | 93.1 (48.4) | −11.8 | 4.4 | −20.4 to −3.3 | 0.01 | | | |
| Ornish | 102.2 (37.1) | −16.6 | 4.4 | −25.2 to −8.1 | 0.0006 | | | |
| **ApoA-I**[m] | | | | | | 0.83 | 0.0007 | 0.001 |
| Atkins | 168.4 (35.7) | 3.0 | 4.0 | −4.7 to 10.7 | 0.45 | | | |
| South Beach | 170.2 (29.3) | 1.8 | 4.0 | −6.1 to 9.6 | 0.67 | | | |
| Ornish | 171.9 (29.8) | −17.8 | 4.0 | −10.1 to −25.6 | 0.0001 | | | |
| **ApoB**[n] | | | | | | 0.05 | 0.006 | 0.37 |
| Atkins | 81.7 (28.9) | 4.8 | 2.7 | −0.45 to 10.0 | 0.08 | | | |
| South Beach | 77.9 (26.8) | −2.9 | 2.7 | −8.3 to 2.4 | 0.29 | | | |
| Ornish | 83.4 (31.0) | −6.4 | 2.7 | −1.2 to −11.6 | 0.02 | | | |
| **CRP**[o] | | | | | | 0.13 | 0.04 | 0.63 |
| Atkins | 0.39 (0.31) | 0.18 | 0.11 | −0.04 to 0.41 | 0.12 | | | |
| South Beach | 0.64 (0.65) | −0.09 | 0.13 | −0.33 to 0.16 | 0.50 | | | |
| Ornish | 0.60 (0.51) | −0.17 | 0.12 | −0.4 to 0.06 | 0.16 | | | |

[a]n=18.
[b]Repeated measures of analysis of variance using general linear modeling for each variable.
[c]Pre=predietary phase baseline.
[d]SD=standard deviation.
[e]SE=standard error.
[f]CI=confidence interval.
[g]Differences between Atkins and South Beach (AS), Atkins and Ornish (AO), and South Beach and Ornish diets (SO).
[h]TC=total cholesterol.
[i]TG=triglyceride.
[j]Log-transformed analysis.
[k]HDL=high-density lipoprotein.
[l]LDL=low-density lipoprotein.
[m]ApoA-I=apolipoprotein A-I.
[n]ApoB=apolipoprotein B.
[o]CRP=C-reactive protein.

drew due to logistical reasons or inability to continue with a specified dietary phase. Mean age was 30.6±9.6 years, and mean body mass index was 22.6±3. Mean fasting lipids and lipoproteins included total cholesterol of 184.9±48.3 mg/dL, triglycerides of 78.1±32.7 mg/dL, low-density lipoprotein (LDL) cholesterol of 107.2±48.3 mg/dL, and HDL cholesterol of 62.2±17.0 mg/dL.

Baseline dietary composition was most consistent with a Mediterranean-like diet with mean total fat intake of 30%±10%. Dietary intake estimates of 72-hour food records demonstrated no appreciable change in energy intake between the Atkins (7,216±1,844 kJ/day), South Beach (6,732±1,338 kJ/day), and Ornish (6,869±1,380 kJ/day) phases consistent with the absence of weight loss.

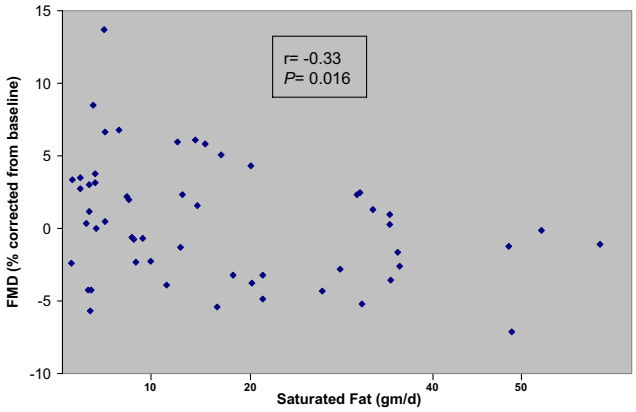


**Figure.** Inverse correlation between saturated fat intake (g/day) and flow-mediated vasodilation (FMD) after correcting for baseline values.

However, the Atkins diet was associated with a greater intake of dietary cholesterol compared to South Beach or Ornish (567±267 vs 202±186 and 114±89 mg/day; $P<0.05$) as well as higher total fat (58±9 vs 31±11 and 9±3; $P<0.001$) and saturated fat content (30±8 vs 14±7 and 3±1; $P<0.001$) compared to the other two dietary phases. The Table outlines predietary phase baseline after the 4-week washout phase and the respective post-dietary changes following each assigned 4-week phase. There were no appreciable differences between baseline levels of lipids, lipoproteins, or apolipoproteins in the three predietary phases. However, total cholesterol and LDL cholesterol were reduced after the South Beach and Ornish phases, whereas apolipoprotein B and apolipoprotein A-I were only reduced after Ornish. When comparing the three dietary phases, the Atkins diet evidenced greater increases in total cholesterol and LDL cholesterol compared to either South Beach ($P=0.007$, $P=0.003$) or Ornish ($P<0.0001$, $P=0.0004$). In contrast, the Ornish diet was associated with reduced HDL cholesterol and apolipoprotein A-I compared to either Atkins ($P=0.01$, $P=0.0007$) or South Beach ($P=0.01$, $P=0.001$), and lower levels of C-reactive protein ($P=0.04$) compared to Atkins dietary phase.

Baseline measurements of brachial artery FMD were similar in the Atkins (3.18±0.59 mm), South Beach (3.16±0.58 mm), and Ornish (3.18±0.64 mm) diets. However, after the assigned dietary period, the Ornish diet was associated with higher FMD compared to Atkins and a nonsignificant increased FMD was also observed after the South Beach diet compared to Atkins. An inverse correlation between on-treatment FMD and saturated fat intake is illustrated in the Figure and an inverse trend was observed between FMD and total fat intake ($r=-0.22$; $P=0.12$).

The most noteworthy finding in the present study was that during weight maintenance, the Atkins diet was associated with higher total cholesterol and LDL cholesterol compared to the South Beach and Ornish dietary phases and reduced endothelial vasoreactivity compared to the Ornish phase. Moreover, saturated fat intake correlated inversely with endothelial function as assessed by brachial artery reactivity testing. Previous isocaloric studies have demonstrated that a low-fat, high-carbohydrate diet is associated with elevation in triglycerides and reductions in LDL cholesterol and HDL cholesterol compared to higher total and saturated fat intake (11,12). Surprisingly, however, there have been minimal isocaloric comparative evaluations of lipids and endothelial function. One study compared a diet high in carbohydrates (18% fat) to high saturated fat (37% fat), monounsaturated fat (37% fat), and polyunsaturated fat (36% fat) each for a 3-week intervention period. Substantial reductions in brachial FMD were observed during the high saturated fat diet phase (4), although the short testing interval without a washout and lack of adjustment for covariates (13-15) may have impacted the modest effects observed. Because most dietary studies are relatively short term (ie, less than 1 year) and focus on weight reduction efficacy, considerably less information is available regarding the potential clinical impact of popular diets after weight has been stabilized (ie, long-term maintenance). Results of the present study suggest that a diet that exhibits unfavorable effects on lipids and endothelial function during the maintenance phase may be less advantageous compared with diets associated with improvement in these parameters. This is particularly noteworthy in subjects at increased risk of CHD (eg, metabolic syndrome) (16), for whom long-term dietary recommendations are often required.

There are several limitations associated with the present study. First, the study was not designed to compare the weight-loss effects of popular diets, but rather to evaluate the biological effects that occur during weight maintenance in apparently metabolically healthy nonobese men and women. Therefore, the study results are neither generalizable to obese subjects nor to those enrolled in the weight-loss induction phase of these diets. Secondly, although lipid- and endothelial-related differences between the dietary phases were discernible despite a relatively small size, C-reactive protein measurements displayed greater variability, suggesting that a larger sample size would be required to better delineate differences between the groups during the maintenance phase. A third limitation relates to verification of adherence to dietary therapy. Specifically, it is recognized that weight monitoring and dietary food records, the primary tools used in the present study, are less sensitive when compared with more reliable methods, such as having assigned dietary meals prepared in a metabolic kitchen.

## CONCLUSIONS

High saturated fat intake may adversely impact lipids and endothelial function during weight maintenance. As such, popular diets such as Atkins may be less advantageous for CHD risk reduction when compared to the Ornish and South Beach diets once weight loss has been achieved. The findings support additional study, especially in subjects with or at increased risk of CHD, in order to further explore the potential clinical implications of popular diets during long-term maintenance.

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# Appendix C:

## Task #10 Manuscripts

# Reducing Perceived Stress Improves Sleep Quality—A Longitudinal Outcomes Study

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**Introduction:** Anecdotal experience suggests that stress is a major impediment to sleep, eroding overall sleep quality. Clinical programs universally endorse interventions for stress reduction to improve sleep, but there are few reports validating this therapeutic approach. To examine the relationship between stress reduction and sleep improvement, we measured changes in perceived stress and its correlation with sleep quality in a longitudinal outcomes study.
**Methods:** The Integrative Cardiac Health Project (ICHP) is a heart health program with goals of improving diet, exercise, sleep and stress. At program entry and at graduation, participants were assessed with the Perceived Stress Scale (PSS14) and the Pittsburgh Sleep Quality Index (PSQI) which includes sleep duration along with sleep latency, sleep fragmentation, perceived restfulness, daytime functioning, nocturnal behaviors, and use of sleep aids. Subjects were divided into groups that improved PSS score and those that did not. Differences between groups were compared using unpaired t-test.
**Results:** 66 consecutive graduates (mean age 59.6+11.6, 28 men) reduced their PSS 3.1$\pm$5.8 points and improved their PSQI 1.2$\pm$2.9 points. Fifty subjects were able to reduce their PSS by a mean of 5.5$\pm$4.5 points accompanied by improvements in PSQI (1.9$\pm$3.0 points), Lp-PLA2 (41.6$\pm$53.8 mg/dL), glucose (2.0$\pm$9.1 mg/dL), insulin (2.2$\pm$7.0 ug/dL) and HOMA (0.04$\pm$1.69). The other 16 subjects showed increases in PSS of 4.3$\pm$2.0, $p<0.001$ accompanied by worsening PSQI (0.27$\pm$2.49, $p=0.02$), Lp-PLA2 (21.7$\pm$65.5, $p=0.02$), glucose (2.8$\pm$11.0, $p=0.08$), insulin (1.4$\pm$6.1, $p=0.07$) and HOMA (0.49$\pm$1.51, $p=0.04$).
**Conclusions:** Reductions in perceived stress correlate significantly with improvements in sleep quality. Improvements in perceived stress and sleep quality are accompanied by improvements in cardiovascular risk markers including glucose metabolism and lipids. Our findings underscore the importance and value of utilizing stress management techniques as a teachable sleep improvement intervention.

**Journal Citation:** Eliasson A, Kashani M, Mayhew M, Ude A, Hoffman J, Vernalis M. Reducing Perceived Stress Improves Sleep Quality—A Longitudinal Outcomes Study. CHEST 2010; 137:913A

# Improving Sleep Quality Correlates with Lower Weight —A Longitudinal Outcomes Study

Arn Eliasson MD, Mariam Kashani CRNP, Maren Mayhew CRNP, Marina Vernalis DO

**Introduction:** Numerous cross-sectional studies have shown an association between shorter total sleep time (TST) and increased weight. However, longitudinal studies examining weight as a function of TST have shown mixed results. In order to examine the relationship between sleep and weight loss, we measured sleep quality rather than TST alone in a longitudinal outcomes study.
**Methods:** The Integrative Cardiac Health Project (ICHP) is a heart health program with goals of improving diet, exercise, sleep and stress. At program entry and at graduation, participants were weighed and completed the Pittsburgh Sleep Quality Index (PSQI) which includes sleep duration along with sleep latency, sleep fragmentation, perceived restfulness, daytime functioning, nocturnal behaviors, and use of sleep aids. Subjects were divided into groups that improved PSQI score and those that did not. Differences between groups were compared using unpaired t-test.
**Results:** 78 consecutive graduates completed ICHP at a mean of 9.4$\pm$2.7 mo. Nine subjects had a body mass index (BMI) <25 kg/m$^2$ at enrollment and were excluded from analysis. The other 69 graduates were overweight (mean BMI=31.1$\pm$5.0 kg/m$^2$), had a mean age of 59.0$\pm$12.7 yrs, included 31 men (45%), and were racially diverse (34 Caucasian, 30 African-American, 4 Hispanic, and 1 Asian). Of these 69 participants, 43 (age 58.2$\pm$13.4 yrs, 17 or 40% men) showed mean improvement in PSQI of 3.5$\pm$3.1 points along with mean decrease in BMI=0.74$\pm$1.3 kg/m$^2$. In contrast, 26 subjects (age 60.5$\pm$11.6 yrs, 14 men or 54%) showed worsening PSQI score of 1.2$\pm$1.4 points and a limited decrease in BMI=0.09$\pm$1.01, p=0.04.
**Conclusions:** In overweight subjects, improvements in sleep quality correlated with greater weight loss. Global assessment of sleep quality, rather than a focus on TST alone, may clarify the mechanism between sleep and weight loss. Identifying these components of sleep quality also provides targets for therapeutic intervention.

**Journal Citation:** Eliasson AH, Kashani M, Mayhew M, Vernalis M. Improving sleep quality correlates with lower weight—A longitudinal outcomes study. Sleep 2010; 33:A378

**Prediabetics Improve CV Risk Profile by Reducing Stress**

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**Background**: High stress levels trigger a negative cascade of hormones mediated in part by cotropin-releasing factor, CRF. The effect of CRF on cortisol is well known but recent science has demonstrated its pivotal role on insulin levels as well. Currently, pharmacologic agents are being developed to assist patients with this proposed hyperinsulinemia.

**Objective:** We sought to examine the effect of stress along with its hormonal mediators on a prediabetic population.

**Methods**: Subjects entering a 6-month cardiovascular (CV) risk reduction program (to improve sleep, exercise, nutrition and stress) completed questionnaires including the Perceived Stress Scale (PSS), anthropometric measures and a cardiac-relevant lab panel. Differences between subjects with high stress (PSS$\geq$23) and those with low stress (PSS<23) were analyzed by t-test.

**Results**: Of 24 prediabetic subjects, 12 (50%) scored high on the PSS (mean 29.5$\pm$4.9 vs 18.4$\pm$3.3). These high-stress subjects demonstrated higher mean insulin (20.6$\pm$11.7 vs 10.8$\pm$4.2, p<0.01), higher insulin resistance, as demonstrated by HOMA, (5.3$\pm$2.9 vs 2.8$\pm$1.2, p<0.01) and greater percent body fat (38.8$\pm$7.6 vs 30.7$\pm$8.5, p<0.02), than their low-stress counterparts. There were no differences in glucose or weight between the two groups at baseline.

| **Change at 6 mo** | **Low stress n=12** | **High stress n=12** | **p value** |
|---|---|---|---|
| PSS 1.4+ | _8.3 -14.4+ | _9.3 <0 | .01 |
| Insulin (ug/dL) | 3.4$\pm$7.7 -11.8+ | _11.8 <0.01 | |
| CRP (mg/dL) | 0.3$\pm$0.41 -0 | .2$\pm$0.7 <0 | .03 |

**Conclusion**: High stress correlates with numerous unhealthy metabolic states which place patients at higher risk for CV disease. Prediabetic patients can significantly improve their CV risk profile by reducing stress. We hypothesize that an integrative lifestyle change program may interrupt the negative sequence of events caused by CRF and potentially provide prediabetic patients an adjunct to their CV risk reduction action plan.

**Journal Citation:** Kashani M, Eliasson A, Vernalis M. Prediabetics improve CV risk profile by reducing stress. Circ Cardiovasc Qual Outcomes 2010; 3:P58

# Longer Sleep Time Confers Cardiovascular Health Benefit

Arn Eliasson MD, Mariam Kashani CRNP, Marina Vernalis DO
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**Background:** Prior research using actigraphy as an objective measure of sleep time showed correlation between short sleep duration and increased BMI. This work was limited by a small cohort and a restricted number of measured parameters. We sought to further examine the relationship between sleep, maintenance of healthy weight, and cardiovascular (CV) health by utilizing validated sleep questionnaires and self-reported sleep time in a larger cohort.

**Methods:** Consecutive subjects entering a 6-month integrative healthy lifestyle program completed questionnaires including the Berlin Questionnaire for sleep apnea risk, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Fatigue Scale and Perceived Stress Scale (PSS). Data collection also included anthropometrics and cardiac-relevant lab panel. Differences between subjects with short sleep (total sleep time or TST $\leq$ 5 hrs/night) and long sleep (TST $\geq$ 7 hrs/night) were analyzed by t-test.

**Results:** In 478 participants (age 54.1$\pm$12.4y, 36% men, 169 Caucasian, 121 African-American, 22 Hispanic, 3 Asian, 12 other, 151 undeclared), Berlin Questionnaire indicated high risk for sleep apnea in 53%. Group TST=6.3$\pm$1.3h; Sleep Latency (SL)=23.6$\pm$38.4 min; PSQI=7.0$\pm$4.3; ESS=8.9$\pm$5.0 and Fatigue=4.3$\pm$2.5; mean BMI=29.8$\pm$5.8; PSS=22.4$\pm$8.1. For 108 short sleepers (age 50.0$\pm$13.0y), Berlin Questionnaire indicated high risk in 66% of subjects; TST=4.5$\pm$0.7h; SL=45.9$\pm$69.0 min; PSQI=10.9$\pm$3.9; ESS=10.7$\pm$5.3 and Fatigue=5.7$\pm$2.2; mean BMI=31.3$\pm$6.5; PSS=24.9$\pm$8.7; and hsCRP=0.44$\pm$0.55 mg/L. By contrast, the 175 long sleepers, were older (57.2$\pm$11.7y, $p<0.001$); had lower % of subjects at risk for sleep apnea (42%); slept longer (TST=7.6$\pm$0.8h, $p<0.001$); fell asleep more quickly (SL=15.2$\pm$14.3 min, $p<0.001$); had better sleep quality (PSQI=4.6$\pm$3.6, $p<0.001$); had less daytime sleepiness (ESS=7.2$\pm$4.8, $p<0.001$); and less fatigue (Fatigue=3.3$\pm$2.6, $p<0.001$). Long sleepers also weighed less (BMI=29.1$\pm$6.0, $p=0.004$); experienced lower stress levels (PSS=20.4$\pm$7.3, $p<0.001$); and had lower levels of the inflammatory marker hsCRP (0.32$\pm$0.47 mg/L, $p=0.05$). Importantly, there were no differences in lipids, glucose or HgbA1C between short and long sleepers.

**Conclusions:** Participants who slept longer showed a better CV risk profile and enjoyed higher quality of life by a number of indicators. Despite a lack of difference in the more traditional risk factors, total sleep time is strongly associated with lower stress, healthier body weight, and lower inflammation. These findings underscore the importance of addressing adequate sleep time as a modifiable risk factor in an integrative program for CV risk reduction.

**Journal Citation:** Eliasson A, Kashani M, Vernalis M. Longer sleep confers cardiovascular health benefit. Am J Respir Crit Care Med 2010; 181:A6524

# Assessing Perceived Stress Provides Targets for Stroke Prevention

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**Background**: Stroke prevention traditionally targets cholesterol and blood pressure control. While these measures are valuable, this limited focus may overlook other variables that increase risk for stroke.
**Objective**: We sought to examine a broader approach to stroke prevention in an integrative cardiovascular prevention program (CPP) by identifying multiple behavioral factors associated with stroke risk. Our integrative program targets cardiovascular (CV) risk reduction through behavioral interventions to improve nutrition, exercise, sleep and stress.
**Methods**: Subjects entering the CPP completed questionnaires including the Perceived Stress Scale (PSS), Epworth Sleepiness Scale (ESS), Fatigue Scale, Pittsburgh Sleep Quality Index (PSQI) and Berlin Questionnaire for Sleep Apnea. Data collection also included anthropometrics and a CV-relevant lab panel. Differences between subjects with high stress (PSS$\geq$23) and those with low stress (PSS<23) were analyzed by t-test.
**Results**: Of 351 consecutively enrolled subjects: 166 (47%) scored above the median PSS. These high-stress subjects displayed an increased cardiovascular risk profile including elevated BMI (31.1$\pm$5.9 vs 29.0$\pm$5.9, p=0.001), increased Waist Circumference (101.5$\pm$17.4 cm vs 98.2$\pm$13.8, p=0.04), glucose (98.1$\pm$28.2 mg/dL vs 92.8$\pm$14.6, p=0.03) and Lp-PLA2 (strongly associated with stroke risk, 220.6$\pm$104.7 ng/mL vs 195.6$\pm$67.1, p=0.02). High-stress subjects also demonstrated greater daytime sleepiness (ESS=10.4$\pm$5.1 vs 7.8$\pm$4.8, p<0.001), greater fatigue (5.4$\pm$2.2 vs 3.4$\pm$2.4, p<0.001), lower sleep quality (PSQI 8.5$\pm$4.4 vs 5.9$\pm$4.0, p<0.001) and shorter sleep duration (19 min less/24 hr, p=0.04) with a higher risk for sleep apnea (60% at high risk vs 41%, p=0.003) than their low-stress counterparts.
**Conclusions**: Assessing stress levels in patients can provide targets for intervention in stroke prevention. High stress is associated with numerous behavioral, biochemical and anthropometric factors that increase stroke risk. Comprehensive stroke risk prevention could benefit from an integrative approach that includes lifestyle behavioral assessment to identify as well as to reduce stroke risk and improve quality of life indicators.

**Journal Citation:** Kashani M, Eliasson A, Hoffman J, Vernalis M. Assessing perceived stress provides targets for stroke prevention. Stroke 2010; 41:e292

# Small Amounts of Regular Exercise: A Lifetime Investment in Weight Management

Ellen Turner, Mariam Kashani, Arn Eliasson, Marina Vernalis

**Background:** Weight gain has traditionally been regarded as an inevitable part of aging. The negative health consequences of weight gain are well known and successful efforts to avoid this pattern would pay health dividends. We sought to evaluate differences in exercise habits and health parameters between subjects who had gained substantial weight compared to those who had limited weight gain over their lifetime.

**Methods:** Subjects entering a healthy lifestyle change program completed the International Physical Activity Questionnaire (IPAQ), were weighed and asked to recall weight at age 18 yrs. Body composition, fasting plasma glucose (FPG) and HDL cholesterol were also measured. Differences between high gainers (HG, those who gained $\geq$1 lb/year) and low gainers (LG, those who gained <1 lb/year) were analyzed by t-test.

**Results:** HG had less total exercise (1022$\pm$1107 MET-min/week) than LG (1353$\pm$1695 MET-min/week) with a difference of 331 MET-min/week (p=0.05). Paradoxically, HG were younger (53$\pm$9 yrs) than LG (62$\pm$10 yrs, p<0.001), gained more weight (75$\pm$34 lbs vs 25$\pm$14 lbs, p<0.001) and body fat (38$\pm$9 % vs 30$\pm$7 %, p<0.001), and had higher FPG (98$\pm$21 mg/dL vs 93$\pm$14 mg/dL, p=0.45) and lower HDL (57$\pm$18 mg/dL vs 64$\pm$21 mg/dL, p=0.004).

**Conclusions:** Despite age, small amounts of exercise per week (the equivalent of 5 days/week of walking 20 min) can result in large differences in weight gain and improved parameters of the cardiovascular profile, such as % body fat, glucose metabolism and cholesterol profile. These findings suggest that exercise can potentially provide a lifetime investment with dividends in improved weight management and heart health.

**Journal Citation:** Turner E, Kashani M, Eliasson A, Vernalis M. Small Amounts of Regular Exercise: A Lifetime Investment in Weight Management. Obesity 2009; 17:S136

# The Need for Cardiovascular Prevention in Young Military Service Members

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Walter Reed Army Medical Center and Jackson Foundation for the Advancement of Military Medicine, Washington, DC

**Background:** Recent data suggest worrisome trends in the prevalence of risk factors for atherosclerosis in Active Duty (AD) soldiers.

**Objective:** We sought to examine CV risk in a group of young AD members.

**Methods:** 14 AD soldiers completed Carotid Intimal Medial Thickness measurement (CIMT--a measure of atherosclerosis), IPAQ (international physical activity questionnaire), BMI, and labs. Differences between subjects with normal and abnormal CIMT (>75% for gender and age) were analyzed by t-test.

**Results:** Of 14 participants (9 men), average age 27.7 years, 5 had abnormal CIMT. These five soldiers exercised less (524$\pm$183 MET-min/week versus 1577$\pm$1253, p=0.10), showed more snoring/OSA (60% versus 11%, p=0.05), weighed more (BMI=32.4$\pm$5.6 kg/m$^2$ versus 28.8$\pm$4.0, p=0.18), had dyslipidemia (100% versus 33%, p=0.01), lower HDL (43.2$\pm$11.8 mg/dL versus 55.7$\pm$11.4, p=0.08), and lower vitamin D (12.5$\pm$4.7 pg/mL versus 20.0$\pm$7.9, p=0.08).

**Conclusion:** In this cohort of young soldiers, subclinical atherosclerosis was prevalent. Reversible risk factors were identified with easily obtained and inexpensive assessment tools. Our experience supports earlier assessment and prevention to conserve the Fighting Force.

# Should Subclinical Hypothyroidism Be Treated to Lower Cardiovascular Risk?

Maren Mayhew MS, CRNP, Arn Eliasson MD, Mariam Kashani MS, CRNP, Marina Vernalis DO

**Background:** Subclinical hypothyroidism (SCH) is diagnosed when TSH is mildly elevated but thyroid hormone levels are normal. Treatment guidelines endorse individualized therapy, offering thyroid replacement for SCH only when symptoms of hypothyroidism are clinically convincing. However, SCH has been associated with increased risk of coronary heart disease (CHD) and while controversial, research has shown that replacement therapy may improve CHD risk factors. In order to inform therapeutic decisions in our cardiovascular disease prevention program (CPP), a program managed by Nurse Practitioners, we sought to evaluate the important health associations of SCH in subjects entering our CPP.

**Methods:** Patients entering our CPP through self-referral or referral by a provider are evaluated by a Nurse Practitioner with history and physical examination, anthropometrics, a panel of laboratory tests, and validated questionnaires assessing sleep behaviors and stress levels. Consecutive patients over a two year period were considered in this analysis. Patients with the diagnosis of overt thyroid disease and patients on thyroid replacement therapy were excluded. Using a TSH cutoff of >4.2 uIU/dL, subjects with SCH were compared with patients whose thyroid panel was normal, using unpaired t-tests. Relationships between TSH and other continuous clinical variables were assessed with the Spearman's rank-order correlation.

**Results:** Of 340 consecutive patients, 51 (15%) were excluded for diagnosed thyroid disease or thyroid replacement medication. The remaining 289 patients (165 women) comprised the study set with 111 Caucasian, 89 African-American, 12 Hispanic, 2 Asian and 75 undeclared. There were 10 patients (3.5%) with SCH (6 women, mean TSH 4.74$\pm$0.41) and 279 patients with normal thyroid studies (158 women, mean TSH 1.78$\pm$0.82). For patients with and without SCH, two sample t-tests showed no differences in BMI, waist circumference, perceived stress levels, or C-reactive protein. Indices of glucose metabolism between groups were not statistically different, including fasting glucose, HbA1c, and HOMA. Compared to normal subjects, patients with SCH showed no differences in sleep habits and symptoms, including sleep latency, sleep duration, habitual snoring, risk for sleep apnea, daytime sleepiness and fatigue. Lipid studies showed no statistical differences in total cholesterol (p=0.55), LDL (p=0.71), HDL (p=0.16), TG (p=0.77), PLA2 (p=0.18) or LPa (p= 0.68). Spearman's rank-order correlation showed a statistically significant inverse correlation between TSH level and LPa (rho= -0.146, p=0.012) and identified a correlation between TSH level and HDL (rho= 0.146, p=0.013). Framingham risk index was not statistically different between patients with SCH and normals (p=0.33).

**Conclusion:** SCH was not associated with an extensive array of CHD risk factors in our population. Our findings support following the current endocrinology guidelines, offering thyroid replacement for SCH only when symptoms of hypothyroidism are clinically compelling. In our Nurse Practitioner managed CPP, the diagnosis of SCH does not appear to warrant thyroid replacement therapy for cardiovascular benefit but should be carefully considered for each patient's circumstances.

# Appendix D:

## Task #10.1 Manuscripts

**Taking Aim at Nurse Stress: A Call to Action**
Mariam Kashani; Arn Eliasson; Linda Chrosniak; Marina Vernalis
*Military Medicine;* Feb 2010; 175, 2; ProQuest Nursing & Allied Health Source
pg. 96

MILITARY MEDICINE, 175, 2:96, 2010

# Taking Aim at Nurse Stress: A Call to Action

*Mariam Kashani, MS, CRNP*; COL Arn Eliasson, USA MC (Ret.)*; Linda Chrosniak, PhD†; COL Marina Vernalis, USA MC (Ret.)**

**ABSTRACT** The study investigates stress levels and related behaviors of nurses in a military medical center during wartime. In 2007, nurses completed a questionnaire survey with objective validation of data in a subsample using actigraphy over 12 weeks. Of 270 nurses, 255 (94%) returned surveys. A total of 81% reported moderately high or high stress with sources listed as work (66%) and fatigue (39%). Many reported coming to work despite feeling ill and/or stressed (13.6 days/3 months). In contrast, morale was high or moderately high in 71%. Nurses reported an average of 5.5 hours of sleep/night, 8.8 h/wk taken for self, and 3.8 h/wk for exercise. Actigraphy data showed an average of 6.0 hours of sleep/night. These findings highlight a mismatch between stress levels and coping perceptions indicating an inability to properly care for self. To manage the effects of chronic stress, nurse leaders should implement systems targeting healthy life balance.

## INTRODUCTION

The central mission of any medical organization is to care for ill and injured patients. The health and welfare of the nursing staff is of paramount importance to accomplish that mission. The work of caring for sick and dying patients along with the high operational tempo of modern and technically advanced medical practice, have a profound impact on the nursing caregivers themselves.[1–3] The stressful work environment often leads to compassion fatigue, potential patient-care errors, absenteeism, and unhealthy behaviors of the caregiver.[4] These unhealthy behaviors can erode physical fitness and exacerbate weight problems, which elevate cardiovascular disease risk.[5,6] Working in this environment may damage the morale of the nursing staff ultimately leading to burnout. From the organization's point of view, recruitment and retention of nurses may be adversely affected.[7,8]

Our medical facility is a large tertiary care military medical center with the mission of caring for soldiers who are ill and wounded in the course of their military duty. The nursing leadership at our institution has been mindful of the increased burden placed on nurses during time of war. The leadership therefore requested an assessment of the emotional state and morale of the members of the staff. The aim of our study was to investigate the state of the nursing staff during war time. We developed a questionnaire to identify pertinent issues placing increased burden on the staff members. In response to the findings of the questionnaire, we sought to capture objective data and actigraphy on a subset of the original population.

## METHODS

### Study Sample and Setting

We administered a questionnaire to the nursing staff at our acute care military medical center in 2007. The questionnaire was distributed to all nurses working on inpatient wards and in outpatient clinics for adult medicine and surgery, gynecology, pediatrics, psychiatry and psychology, intensive care, emergency services, as well as specialty services and clinics where specialized nurses worked. In short, every nurse employed at our medical center was given an opportunity and was encouraged to participate in completing the questionnaire survey. Completion of the questionnaire was voluntary and members of the nursing staff were given privacy and anonymity. The number of questionnaires distributed and collected was tabulated.

*Questionnaire*

The questionnaire asked nurses to note on a scale from 1 to 5 how their morale was, how high their perceived stress was, and to list their sources of stress. Participants were further asked to recall how many days in the previous 3 months they missed work because of illness and to estimate how many days they came to work despite feeling ill. They were also queried on whether they felt they had the tools necessary to cope with stress, tools necessary to follow a healthy diet, and to estimate how much time per week they spent in leisure activities, exercise, and sleep.

The questionnaire was administered to a pilot group of nurses asking for feedback on question clarity and question and answer format issues. Adjustments in the questionnaire were implemented on the basis of feedback from the pilot group leading to a one-page tool with 14 questions.

*Subsample Survey*

To obtain objective data to verify self-reported information from the questionnaire, a 14-member convenience sample of the study population volunteered to wear actigraphy armbands (BodyMedia Sensewear, Pittsburgh, PA) continuously for 12 weeks. The armbands measured body temperature, ambient temperature, position sense, and accelerometry and were programmed to calculate total sleep time (TST), recumbent time, and sleep efficiency (SE). Data downloaded from the actigraphs were averaged and compared with self-reported data.

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The 14-member subgroup of the study population also completed four other validated survey instruments, the Perceived Stress Scale, the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, and a fatigue scale.

The Perceived Stress Scale[9] (PSS)-14 is one of the most widely accepted of measurements of stress. Validation studies show that the PSS-14 has an internal consistency reliability of 0.85 by Cronbach $\alpha$ and a test-retest reliability of 0.85. This 14-item questionnaire asks the subject how often certain experiences of stress occurred in the last month and is designed to measure the degree to which situations in one's life are appraised as stressful. With item responses from 0 to 4, the range of possible scores is 0 to 56 with higher scores correlating with higher stress. The PSS is designed for use in community samples with at least a junior high school education. The items are easy to understand and the response alternatives are simple to grasp. Moreover, the questions are quite general in nature and hence relatively free of content specific to any subpopulation group. Scores in the low 20s reveal moderate stress levels whereas scores approaching 30 are substantial and concerning.

The Pittsburgh Sleep Quality Index (PSQI)[10] is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month interval. Nineteen individual items generate seven component scores whose sum yields one global score with a range of 0 to 21. The psychometric and clinical properties of the PSQI suggest its utility both in clinical practice and research activities. A PSQI greater than 5 has a diagnostic sensitivity of 89.6% and specificity of 86.5% ($\kappa > 0.75$, $p < 0.001$). Essentially, a global score of greater than 5 indicates a poor sleeper. Sleep perturbations can be categorized by the following scores: 0 to 5 is a good sleep score, 6 to 10 shows mild sleep difficulty, 11 to 15 moderate sleep difficulty, and 16 to 21 severe sleep difficulty.

The Epworth Sleepiness Scale (ESS)[11] is the most widely used tool to estimate the subjective symptom of daytime sleepiness. The ESS has a sensitivity of 93.5% and a specificity of 100% for detecting excessive daytime sleepiness. Subjects are asked to use a scale of 0 to 3 to estimate their likelihood of dozing in seven different situations in recent weeks. The individual scores are summed and possible scores range from 0 to 21. Sleepy subjects score 10 or higher and sleepiness can be categorized by the following scores: 10 to 13 mild sleepiness, 14 to 17 moderate sleepiness, and 18 to 21 severe sleepiness.

The Fatigue Visual Numeric Scale is borrowed from the Stanford Patient Education Research Center where it was tested on 122 subjects, with mean value of 4.89 and standard deviations of 2.71.[12] This fatigue scale asks subjects to express their experience of fatigue from 0 to 10 for the previous 2-week period. Subjects who circle 5 to 6 express mild fatigue, 7 to 8 moderate fatigue, and 9 to 10 severe fatigue.

## DATA ANALYSIS

Data were analyzed with Microsoft Office Excel 2007 (Redmond, Washington). Variables are expressed as means with standard deviation (SD) or with range. Intergroup differences were analyzed using Student's $t$-test for continuous variables and $\chi^2$ test for discrete variables. The significance level was set at $p \leq 0.05$.

## RESULTS

Of 270 nurses who received a questionnaire, 255 (94%) returned surveys. The population was composed of 69% women, 49% married, and racial/ethnic distribution of 51% white, 25% black, 9% Asian, 8% Hispanic, and 7% other.

The salient findings included reports of very high stress in 55% of respondents and moderately high stress in 26% (see Fig. 1). Sources of stress ranked by order of frequency were: work (66%), fatigue (39%), finances (33%), home (25%), and health (18%). These numbers add to a sum greater than 100% because multiple stressors could be noted by each participant. Few nurses reported missed work days for illness and/or stress (average 1.4 days over 3 months), but many reported coming to work despite feeling ill and/or stressed (average 13.6 days over 3 months). In contrast however, morale was scored as high in 47% of respondents and moderately high in 24% (see Fig. 2).

Regarding having necessary tools to cope with stress, 55% affirmed strongly and 21% affirmed moderately strongly that they believed they possessed necessary and appropriate tools to cope with stress (see Fig. 3). In the same vein, 40% of nurses were very confident they could maintain a healthy diet and 26% were moderately confident they could do so. However, respondents averaged 5.5 hours of sleep per night, 8.8 hours per week taken for stress-reducing leisure activities, and 3.8 hours per week taken for exercise. It deserves note that a substantial number of the nursing staff members are serving in active military service and are required to maintain specified fitness levels including passing scores on biannual physical fitness tests.

Actigraphy data were downloaded from armbands worn by the 14-member subgroup of nurses (see Table I). The average

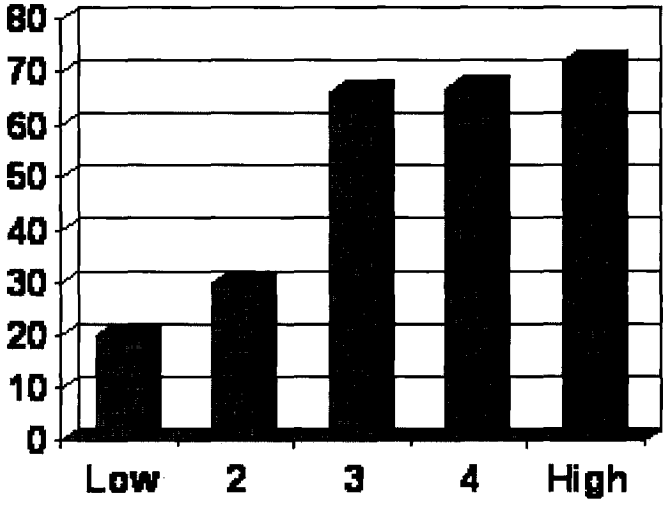


**FIGURE 1.** Self-reported stress levels in 255 respondents.



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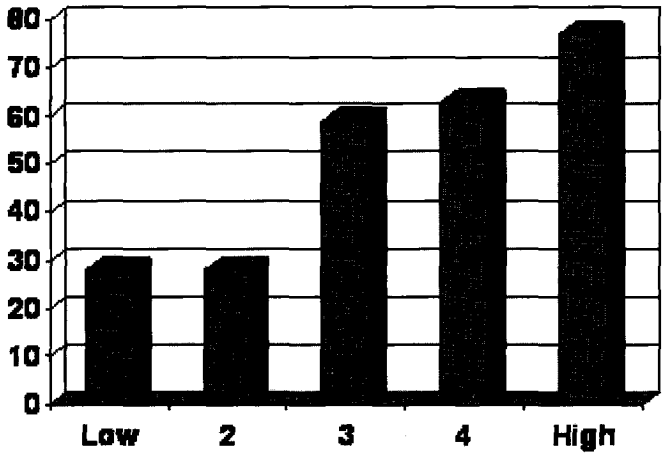


**FIGURE 2.** Self-report on belief in having tools to cope with stress in 255 respondents.

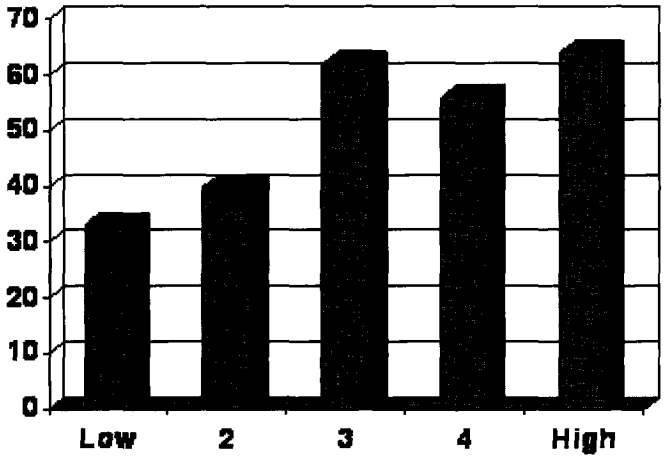


**FIGURE 3.** Self-reported morale in 255 respondents.

age of the 14 nurses (4 men) showed that they were middle-aged. Their self-reported sleep time by questionnaire was substantially less than 7 to 8 hours commonly recommended for most adults. This self-reported sleep time was somewhat less than the objectively measured sleep time but the difference did not reach a statistically significant difference ($p = 0.12$). Mean recumbent time for the group was 7.5 ± 0.7 hours with a calculated sleep efficiency of 80 ± 5%.

The 14-member subgroup of nurses also showed high levels of stress (Table I). Sleep difficulties were evident in 11 of the 14 subjects (79%) with 7 of 14 (50%) in the mild category, 2 of 14 (14%) moderate, and 1 of 14 (7%) severe. Data analysis from the 14-member subgroup of nurses revealed interesting trends (Table II). Five nurses with PSS-14 scores greater than 28 (high stress group) were compared with nine nurses with PSS-14 scores less than 27 (low and moderate stress group). Nurses in the high stress group showed a trend toward being sleepier by the Epworth Score ($p = 0.06$), more fatigued ($p = 0.09$), and with a tendency toward overweight ($p = 0.17$), though these differences did not reach statistical significance.

**TABLE I.** Data From Subgroup Wearing Actigraphy Armbands

| Gender | Age (yrs) | Stress Level | PSQI | Self-Reported Sleep (hr/24 hr) | Sleep (hr/24 hr) Actigraphy |
|---|---|---|---|---|---|
| F | 43 | 30 | 5 | 5.0 | 5.1 |
| F | 38 | 26 | 6 | 5.0 | 6.7 |
| M | 51 | 24 | 12 | 6.0 | 5.6 |
| F | 36 | 29 | 10 | 7.5 | 6.5 |
| F | 57 | 24 | 16 | 4.0 | 6.6 |
| M | 35 | 32 | 10 | 5.0 | 6.2 |
| F | 24 | 23 | 10 | 5.0 | 6.6 |
| M | 42 | 26 | 13 | 6.0 | 5.5 |
| F | 31 | 33 | 6 | 4.0 | 5.7 |
| F | 42 | 22 | 7 | 6.5 | 6.3 |
| F | 42 | 33 | 9 | 5.5 | 6.4 |
| M | 21 | 26 | 5 | 6.0 | 5.2 |
| F | 23 | 22 | 5 | 5.0 | 4.8 |
| F | 32 | 24 | 9 | 6.0 | 6.5 |
| Average $n = 14$ | 36.9 | 26.7 | 8.8 | 5.5 | 6.0 |
| Standard Deviation | 10.4 | 4.0 | 3.4 | 0.9 | 0.7 |
| | | | | $p = 0.12$ | |

Stress level measured using the Perceived Stress Scale (PSS-14, see Methods). PSQI (Pittsburgh Sleep Quality Index) is a global measure of sleep quality and quantity formulated to produce a single score. (See Methods section for details.)

## DISCUSSION

Caring for others is central to the definition of nursing. While nurses show commitment to others, including concern for immediate and extended family,[13] they frequently neglect to care for themselves. With the focus on others, nurses often forego self-assessment[14,15] and the corresponding benefit from renewal activities.[16] Ultimately, nurses tend to overestimate their ability to sustain a productive pace.

The most prominent findings of our questionnaire survey were that stress levels, largely from work, were dramatically elevated in this nurse population in curious counterpoint to remarkably high morale and a strong degree of confidence in their ability to cope. This mismatch is underscored by the low amount of time spent on themselves per week and the few hours of sleep obtained at night. These data indicate an unsustainable lifestyle schedule and are similar to previously reported findings in this population.[17]

The mismatch observed in our nurse population mirrors the physiological mechanism of a type-II diabetic patient whose chronic disease renders cells insensitive to insulin leading to an unhealthy metabolic state. Similarly, nurses under chronic stress and on a path toward burnout may be unable to mount a healthy stress response.[18] Much like a physiological environment lacking proper homeostasis, our nurse data reflect an inability to self-regulate demonstrated by unhealthy lifestyle choices in a chaotic work place.

The presence of high morale may mislead supervisors in the chain of command at military institutions to overlook signals of personnel distress. In the military, the culture is different than that of a civilian facility. The military medical team is



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**TABLE II.** Comparison Between Stress Levels, Daytime Symptoms, and BMI

| Group $n = 14$ | Gender (% Male) | Age (yrs) | Stress Level | Epworth Sleepiness | Fatigue Scale[a] | BMI (kg/m$^2$) |
|---|---|---|---|---|---|---|
| More Stressed $n = 5$ | 20% | 37.4 ± 5.0 | 31.4 ± 1.8 | 14.0 ± 6.0 | 6.4 ± 2.1 | 28.5 ± 6.1 |
| Less Stressed $n = 9$ | 30% | 36.7 ± 12.7 | 24.1 ± 1.6 | 7.3 ± 5.9 | 4.1 ± 2.3 | 24.9 ± 3.3 |
| $p$ value | 0.62 | 0.90 | <0.001 | 0.06 | 0.09 | 0.17 |

For details on measurements of stress level, Epworth Sleepiness Scale, and fatigue scale, see Methods section.
[a]Fatigue Visual Numeric Scale.

imbued with a unique allegiance to accomplish the mission at hand despite personal obstacles such as fatigue and burnout. It is critically important that the leadership recognize the long-term effects of this military culture of self-sacrifice for the greater good. Leaders must survey their charges for unsustainable personal lifestyle habits before burnout occurs.

A unique aspect of our study is that the subjective self-reported information was substantiated with data from validated questionnaires and objective information from actigraphy in a subset of the study population. Question 1 of the Needs Assessment Survey asked subjects to rate their stress level on a Likert Scale from 1 to 5 (high stress levels are graphically reported in Fig. 1). This was substantiated in the 14-member subgroup where PSS scores averaged 26.7, values that demonstrate a concerning elevation in stress levels. Similarly for sleep, question 10 asked "On average, how many hours do you sleep each night?" The nurses in the subgroup self-reported their sleep time as 5.5 hrs/night, not statistically different from 6.0 hrs/night as measured with actigraphy.

Of importance, our study showed interesting trends to support the notion that nurses who feel more stressed, also feel sleepier, are more fatigued, and tend to be more overweight. These findings add to our understanding of the cascade effect of poor lifestyle choices: that stress begets poor sleep that leads to more impairing daytime symptoms that in turn lead to dysfunctional lifestyle choices. This self-reinforcing negative cascade may create other vulnerabilities such as cardiovascular disease, chronic sleep disruption, depression, and a negative self-image. Research has shown that risky behaviors tend to cluster with other risk-promoting choices.[19] It is never too early to intervene upon this negative sequence, previously described as loss spirals.[20]

The utility of actigraph recordings derives from the very nature of sleep, a state of unconsciousness with a lack of awareness of the timing of sleep onset and wakefulness. These facts make estimations of sleep time vulnerable to inaccuracies increasing the value of objective measures of sleep. Actigraphy provides an objective measure of total sleep time. Because actigraphs can be worn for a number of sequential days, estimates of total sleep time include daytime napping behaviors in addition to nocturnal sleep. Furthermore, actigraphy can capture data to describe sleep variability that occurs in weekday and weekend schedules.

The original actigraphs developed in the early 1970s were essentially activity monitors worn on the arm or leg. Actigraphs have since passed through generations of developmental changes. The modern validated actigraph measures a variety of variables including position (e.g., recumbence versus upright posture), motion (including intensity and frequency of movement), body temperature and ambient temperature (to detect drop in body temperature associated with sleep onset). These variables can be utilized to calculate a variety of outputs of interest, most notably highly accurate estimates of total sleep time, sleep efficiency, resting energy expenditure, and exercise energy expenditure. The reliability of actigraphy versus EEG for distinguishing wake from sleep depends on the population studied but in adults with non-pathological sleep, reliability coefficients have ranged from 0.89 to 0.98.[21,22]

The use of actigraphy in clinical medicine and research has flourished. Actigraphy is especially useful in evaluation of insomnia, shift-worker syndrome, and disorders of circadian rhythm where unraveling the particulars of sleep behaviors can be invaluable for diagnosis and management of the condition. Actigraphy has been particularly useful in epidemiological studies where polysomnography is too expensive or impractical in large populations.

Poor behavioral choices on the part of individual nurses have an impact on nursing staff retention. Nurses living and working at such an unsustainable pace are prone to burnout, leading to increased nursing staff turnover.[3] The cost of turnover is felt in terms of economics and quality of care.[23] Nurse turnover costs have been monetarily estimated to be an additional 30% over baseline salary expenditures.[8] Quality of care suffers when institutional memory is depleted and understanding and experience with standard procedures diminish. Team work on a nursing unit is eroded through loss of staff members. In fact, hospital nurse shortages have been linked to higher 30-day patient mortality and higher "failure-to-rescue" rates. Nurses working in this environment are more likely to experience burnout and job dissatisfaction.[4]

High stress levels can potentially paralyze the staff at a military medical facility. Leaders should hear our call to attention as they have the authority and responsibility to safeguard their most important asset, their personnel. Populationwide health systems that use an integrative approach to improve self-care among nurses are successful.[23] Programs that protect medical personnel from the toxicity of wartime must be applied to multiple populations such as chaplains, physicians, physical therapists, and medics to optimize caregiver sustainment.



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Previous obstacles to care in the military have included the stigma associated with mental health services. A program that is labeled "stress reduction" or that is housed in mental health services may be poorly subscribed to. The integration of stress reduction with sleep improvement, exercise promotion, and healthful eating naturally weaves together the mainstays of healthy living and opens doors to preventive care. Stress reduction under the nonstigmatized umbrella of a healthy lifestyle program may not only encourage participation but also build toward a cascade of institutional success.

Limitations of this study include a questionnaire that deserves further work to establish its reliability and validity. Furthermore, until we validate our questionnaire and demonstrate its utility in a civilian population, it would not be proper to generalize our findings to nonmilitary populations because of the unique setting in which our nurses work.

We believe that the stressful healthcare environment, nurse burnout, and the consequent impact on work force retention are problems of growing urgency.[15] The nursing work force is aging even as the complexity of providing care and the speed of technological change are increasing.[24] It is time to raise awareness of the effects of stress in military healthcare workers, especially in time of war, and to take systemwide action to establish integrative interventions to sustain the fighting force.

## CONCLUSIONS

In summary, we take aim at nurse stress with a call to action for nurses to engage in more vigilant and effective self-care. Sustainable schedules along with balance between work and home life must be sought. Achieving this balance depends on the ability of nurses to adopt better self-regulatory strategies that will build resilience. Furthermore, it makes good economic and managerial sense for institutions to invest in their nursing staff by developing and implementing accessible programs to assess and manage stress and to promote a pace of life that can be maintained. Perhaps the Golden Rule for nurses should be, "Care for Yourself as You Care for Others."

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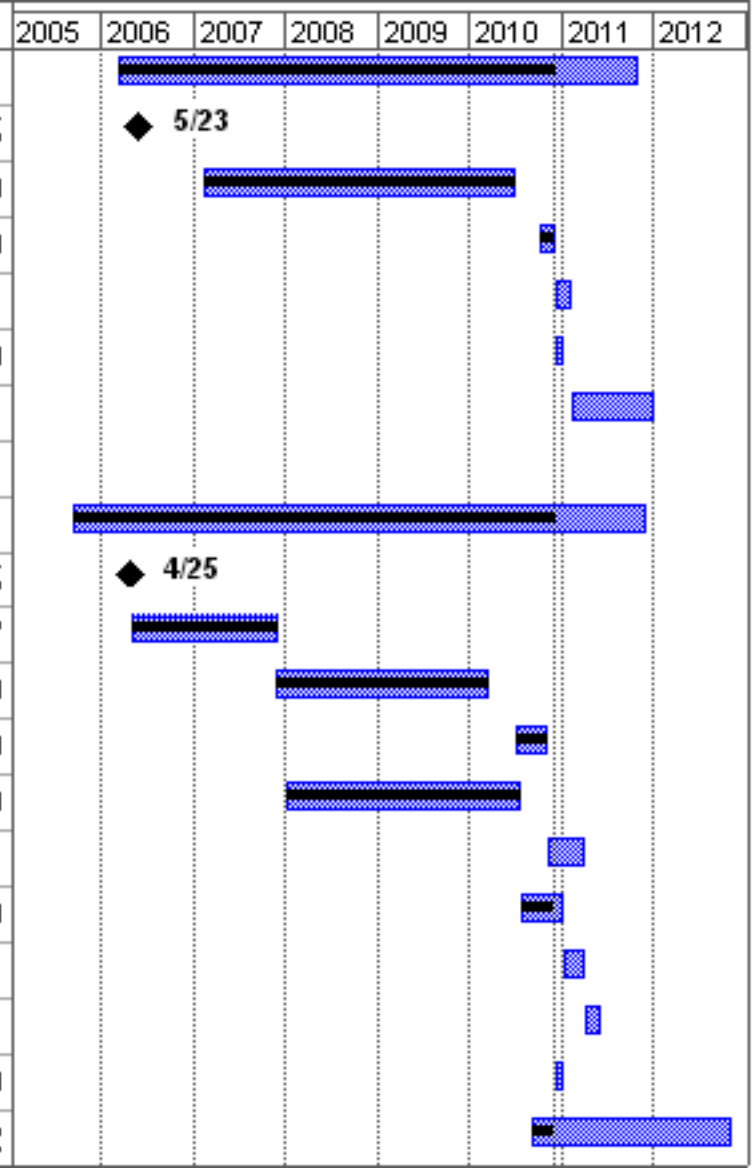
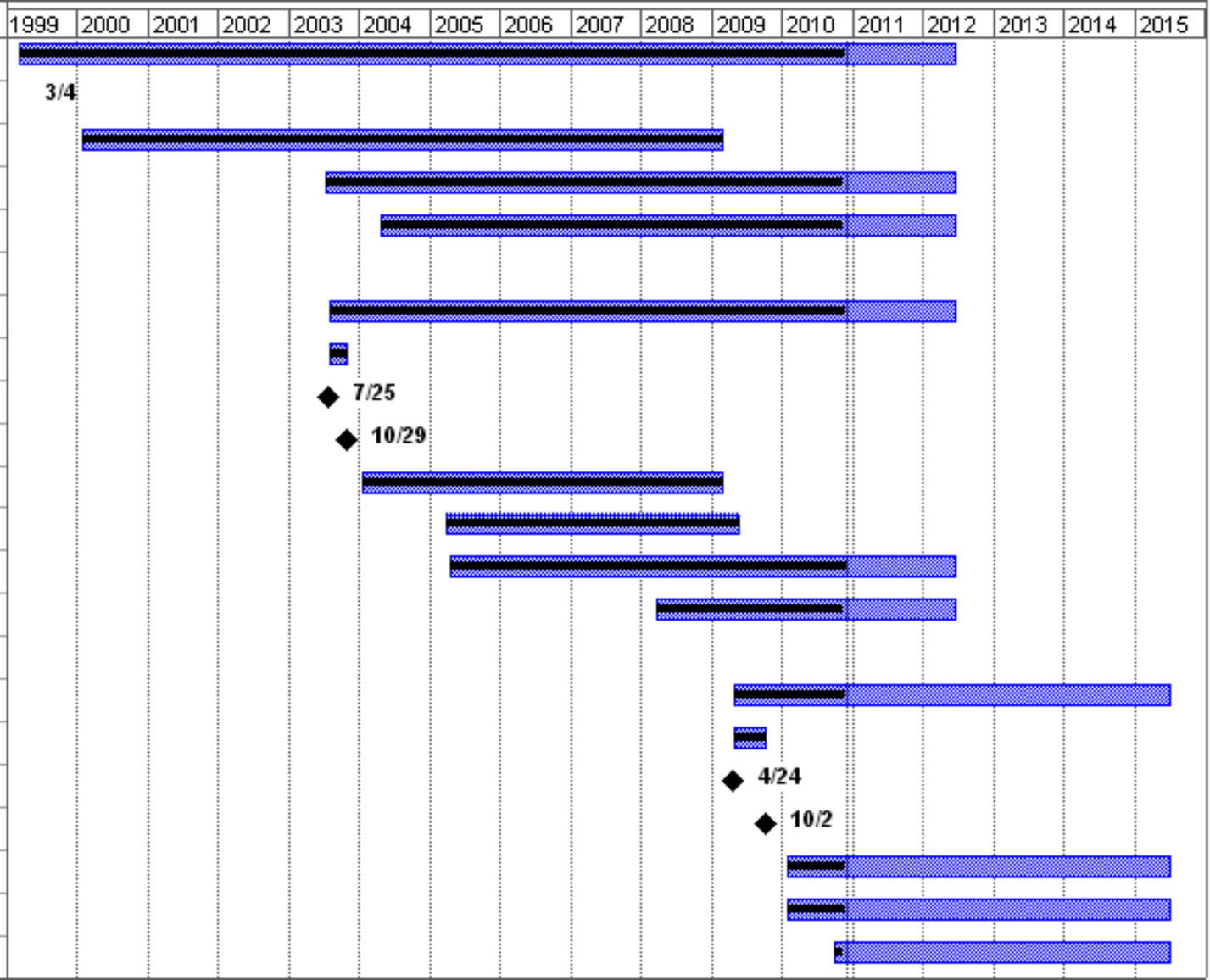
# Appendix E:

Gantt Charts

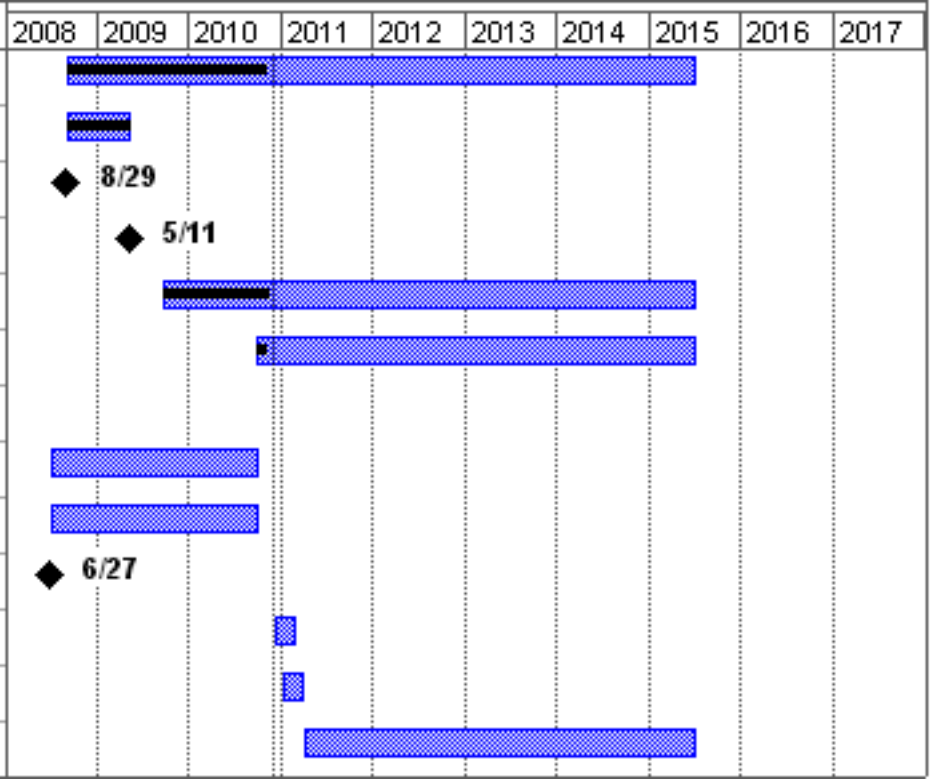
| ID | Task Name | Start | Finish |
|---|---|---|---|
| 1 | Task #3: CADRe Five-Year Follow-up | Wed 3/1/06 | Mon 10/31/11 |
| 2 | IRB protocol approval | Tue 5/23/06 | Tue 5/23/06 |
| 3 | Participant enrollment/Data collection | Fri 2/2/07 | Wed 6/30/10 |
| 4 | Data reconciliation | Fri 10/1/10 | Tue 11/30/10 |
| 5 | Conduct analysis | Wed 12/1/10 | Tue 2/1/11 |
| 6 | Publication plan | Wed 12/1/10 | Fri 12/31/10 |
| 7 | Presentations and manuscripts | Tue 2/1/11 | Fri 12/30/11 |
| 8 | | | |
| 9 | Task #4: BATTLE trial | Thu 9/1/05 | Wed 11/30/11 |
| 10 | IRB protocol approval | Tue 4/25/06 | Tue 4/25/06 |
| 11 | Intervention preparation | Tue 4/25/06 | Fri 11/30/07 |
| 12 | Recruitment/Enrollment/Data | Thu 11/15/07 | Wed 3/10/10 |
| 13 | Addendum submission/approval | Thu 7/1/10 | Fri 10/29/10 |
| 14 | Data collection (Main study) | Tue 1/1/08 | Thu 7/15/10 |
| 15 | Data collection (Addendum) | Mon 11/1/10 | Thu 3/31/11 |
| 16 | Database reconciliation (Main study) | Thu 7/15/10 | Fri 12/31/10 |
| 17 | Data analysis (Main study) | Mon 1/3/11 | Thu 3/31/11 |
| 18 | Quantitative analysis (Addendum) | Fri 4/1/11 | Mon 5/30/11 |
| 19 | Publication plan | Wed 12/1/10 | Fri 12/31/10 |
| 20 | Presentations and manuscripts | Wed 9/1/10 | Wed 10/31/12 |



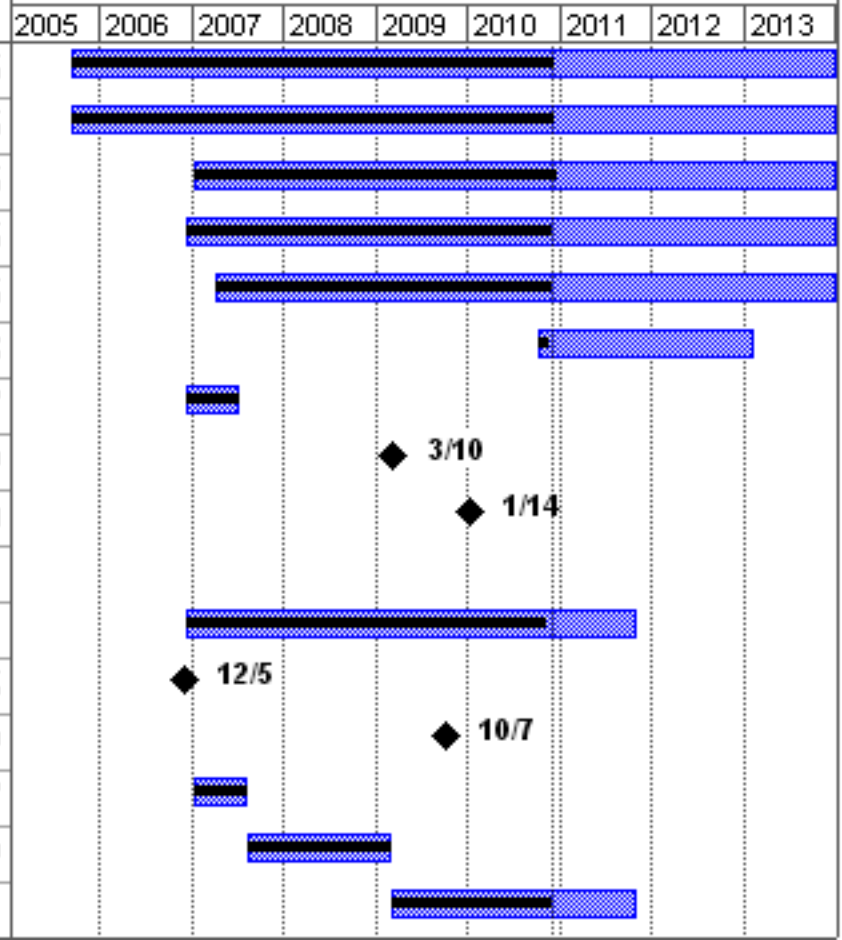
| ID | Task Name | Start | Finish |
|---|---|---|---|
| 1 | Task #5: Ornish Program | Thu 3/4/99 | Fri 6/15/12 |
| 2 | Protocol approved at WMC | Thu 3/4/99 | Thu 3/4/99 |
| 3 | Enroll program participants | Tue 1/25/00 | Wed 2/25/09 |
| 4 | Conduct risk factor analyses | Tue 7/1/03 | Fri 6/15/12 |
| 5 | Presentations and publications | Tue 4/13/04 | Fri 6/15/12 |
| 6 | | | |
| 7 | Task #6: Global Profiling | Fri 7/25/03 | Fri 6/15/12 |
| 8 | IRB protocol development | Fri 7/25/03 | Wed 10/29/03 |
| 9 | Protocol approved at WMC | Fri 7/25/03 | Fri 7/25/03 |
| 10 | Protocol approved at USUHS | Wed 10/29/03 | Wed 10/29/03 |
| 11 | Enroll program participants | Mon 1/12/04 | Wed 2/25/09 |
| 12 | Enroll control subjects | Mon 3/21/05 | Tue 5/19/09 |
| 13 | Conduct molecular analyses | Mon 4/11/05 | Fri 6/15/12 |
| 14 | Presentations and publications | Tue 3/11/08 | Fri 6/15/12 |
| 15 | | | |
| 16 | Task #7: CRC | Fri 4/24/09 | Tue 6/30/15 |
| 17 | IRB protocol development | Fri 4/24/09 | Fri 10/2/09 |
| 18 | Protocol approved at WMC | Fri 4/24/09 | Fri 4/24/09 |
| 19 | Protocol approved at TATRC | Fri 10/2/09 | Fri 10/2/09 |
| 20 | Enroll program participants | Tue 1/19/10 | Tue 6/30/15 |
| 21 | Enroll control subjects | Tue 1/19/10 | Tue 6/30/15 |
| 22 | Conduct molecular analysis | Wed 9/15/10 | Tue 6/30/15 |



| ID | Task Name | Start |
|---|---|---|
| 1 | Subtask #7a: STEP | Fri 8/29/08 |
| 2 | IRB protocol development | Fri 8/29/08 |
| 3 | Protocol approved at WMC | Fri 8/29/08 |
| 4 | Protocol approved at TATRC | Mon 5/11/09 |
| 5 | Enroll program participants | Tue 9/15/09 |
| 6 | Conduct molecular analysis | Wed 9/15/10 |
| 7 | | |
| 8 | Task #9: MI in Young Military | Fri 6/27/08 |
| 9 | IRB protocol development | Fri 6/27/08 |
| 10 | Protocol approved at WMC | Fri 6/27/08 |
| 11 | Protocol approved at WRAMC | Wed 12/1/10 |
| 12 | Protocol approved at TATRC | Fri 12/31/10 |
| 13 | Conduct molecular analysis | Fri 4/1/11 |



| ID | Task Name | Start | Finish |
|---|---|---|---|
| 1 | Task #10: Continuation of CPP/Protocol | Thu 9/1/05 | Wed 9/30/15 |
| 2 | Participant enrollment/Data collection | Thu 9/1/05 | Wed 9/30/15 |
| 3 | Outcomes analysis | Mon 1/1/07 | Wed 9/30/15 |
| 4 | Target subgroup populations | Fri 12/1/06 | Wed 9/30/15 |
| 5 | Presentations and manuscripts | Mon 4/2/07 | Wed 9/30/15 |
| 6 | Upgrade database | Fri 10/1/10 | Thu 1/31/13 |
| 7 | CORPS Project | Fri 12/1/06 | Fri 6/29/07 |
| 8 | Retrospective CPP Outcomes Approval | Tue 3/10/09 | Tue 3/10/09 |
| 9 | Retrospective CPP Outcomes Approval | Thu 1/14/10 | Thu 1/14/10 |
| 10 | | | |
| 11 | Subtask #10.1: Validate ICHP CV risk | Tue 12/5/06 | Fri 10/28/11 |
| 12 | IRB protocol approval | Tue 12/5/06 | Tue 12/5/06 |
| 13 | Continuing review approved | Wed 10/7/09 | Wed 10/7/09 |
| 14 | Data collection | Mon 1/1/07 | Tue 7/31/07 |
| 15 | Conduct analysis | Wed 8/1/07 | Fri 2/27/09 |
| 16 | Presentations and manuscripts | Mon 3/2/09 | Fri 10/28/11 |



## Appendix F
## Integrative Cardiac Health Project - Current Personnel

| WRAMC | | |
|---|---|---|
| **Name** | **Position** | **% of Effort** |
| Marina Vernalis | Medical Director | 80 |
| Audra Nixon | Director, Administration | 80 |
| Arn Eliasson | Senior Physician Research Consultant | 80 |
| Mariam Kashani | Director, Clinical Programs | 80 |
| Elaine Walizer | Clinical Research Coordinator | 100 |
| Maren Mayhew | Nurse Practitioner | 100 |
| Jill Phillips | Nurse Practitioner | 100 |
| Nancy Saum | Research Associate | 100 |
| Adina Bishop | Health Coach | 50 |
| Nancy Tschiltz | Clinical Dietitian | 100 |
| Joy Halsey | Clinical Dietitian | 100 |
| Linda Crosniak | Clinical Psychologist | 100 |
| Ellen Turner | Exercise Physiologist | 100 |
| Jacqueline Hoffman | Stress Mgt Instructor | 100 |
| Karla Bailey | Ultrasound Tech | 100 |
| Lydia Hill | Clinical Admin Project Officer | 65 |
| Josephine Henderson | Administrative Asst | 100 |
| Christa Caporiccio | Administrative Asst | 100 |
| Jill Levin | Research Associate | 100 |

| WRI | | |
|---|---|---|
| **Name** | **Position** | **% of Effort** |
| Daniel Croft | Research Associate III | 85 |
| Darrell Ellsworth | Senior Director | 75 |
| Alisha Decewicz | Research Associate II | 100 |
| David Decewicz | Research Physician | 75 |
| Amber Greenawalt | Research Assistant | 5 |
| Rick Jordan | Casual Employee | 100 |
| Ric Katenhusen | Research Associate II | 5 |
| David Kirchner | Research Associate III | 10 |
| Kumar Kolli | Senior Director | 5 |
| Caroline Larson | Resource Manager | 5 |
| Matthew Masiello | Director, CHP&DP | 8 |
| Richard Mural | CSO | 5 |
| Heather Patney | Research Associate II | 50 |
| Sean Rigby | Research Assistant | 5 |
| Laura Voeghtly | Postdoctoral Fellow | 100 |
| Lydia Furmanchik | Finance Assistant | 15 |
| Lynn Trostle | Grant Coordinator | 15 |
| Amy Burke | Clinical Research Mgr | 70 |
| Mary Jane Haberkorn | Research Nurse | 100 |
| Fran Lechak | Registered Dietician | 100 |
| Kathy Prazich | Data Entry Clerk | 100 |
| Angie Rokita | Exercise Physiologist | 100 |
| Judith Sullivan | Stress Mgmt | 95 |
| James Vizza | Psychologist | 60 |
| TBD Ultra | sound Tech | 50 |
| TBD | Nurse Case Manager | 70 |